New Data Verify Clopidogrel-PPI Interaction

An increased risk for ischemic events has been identified in three recent observational reports.

BY MITCHEL L. ZOLER

Increasing evidence that treatment with a proton-pump inhibitor can reduce the efficacy of clopidogrel in patients with coronary disease in a clinically meaningful and dangerous way may prompt cardiology groups to rethink current recommendations on using the two drugs together.

Although data from "a series of observational reports … are not ideal for clinical decision making, I think we are going to have to readdress the issue," said Dr. Robert A. Harrington, an interventional cardiologist and professor of medicine at Duke University, Durham, N.C.

He was one of several cardiologists who quickly conferred last November, after a talk at the American Heart Association's scientific sessions reported the first clinical evidence of an increased risk for ischemic events in patients with coronary disease on clopidogrel.

Representatives of the American College of Cardiology, the American College of Gastroenterology, and the AHA later that same day issued a statement saying that the evidence from that single study did not provide "sufficient evidence to change clinical practice." But findings in two later reports, the most recent of which appeared in JAMA in early March, changed the minds of some experts.

"The idea of prescribing a PPI as routine practice [in patients on clopidogrel] has to be questioned given the combination of pharmacologic as well as now clinical data. I'm not doing this routinely now without thinking, Does the patient really need the PPI?" said Dr. Eric D. Peterson, also professor of medicine at Duke, and a coauthor of the JAMA report.

Preliminary evidence also suggests that for patients who clearly need a PPI while taking clopidogrel, pantoprazole may be the safest PPI because, unlike other PPIs, it does not inhibit the hepatic enzyme responsible for converting clopidogrel to the active form with an antiplatelet effect.

A special danger may also come from the OTC availability of omeprazole, which patients could start on their own without consulting their physicians. "The burden is on physicians to tell patients that just because a drug is available OTC doesn't make it safe," said Dr. Harrington, also director of the Duke Clinical Research Institute, in an interview.

Physicians often prescribe a PPI to patients taking clopidogrel (Plavix), a mainstay of treatment for patients who have received a coronary stent or have had a recent acute coronary syndrome (ACS) event, because clopidogrel has been linked to gastric bleeding.

Last October, an expert consensus document from the ACC, ACG, and AHA endorsed using a PPI in patients at high risk for gastrointestinal bleeding when on clopidogrel or other agents that can cause duodenal bleeds such as aspirin or NSAIDs (Circulation 2008;118:1894-909).

High-risk patients include those with a history of an ulcer and those on an additional medication that would boost their bleeding risk, such as warfarin or a corticosteroid, said Dr. Deepak L. Bhatt, a cardiologist at Brigham and Women's Hospital in Boston and cochair of the expert panel that wrote the recommendations last October. But many physicians go beyond this recommendation and prescribe a PPI to patients on clopidogrel who are not at high risk.

The new report in JAMA came from an observational study of patients hospitalized for an acute myocardial infarction or unstable angina during October 2003–January 2006 at any of 127 Veterans Affairs hospitals. At discharge, 8,205 of the patients filled a prescription for clopidogrel from a VA pharmacy; 64% also took a PPI at discharge, and the other 36% did not receive a PPI prescription and were presumed not taking one of these drugs. Perhaps as many as 60% of the patients prescribed a PPI at discharge received it without having a bleeding indication and so probably got the drug as prophylaxis only, said Dr. P. Michael Ho, lead author of the study and a cardiologist at the Denver Veterans Affairs Medical Center, in an interview.

A special danger may also come from the over-the-counter availability of omeprazole, which patients could start on their own without consulting their physicians.

During a median follow-up of 521 days, the rate of death or rehospitalization for an ACS event was 21% in patients on clopidogrel only and 30% in those on both clopidogrel and a PPI. In a multivariant analysis that controlled for baseline demographic and clinical variables, patients on both drugs were 25% more likely to die or be rehospitalized for ACS, 86% more likely to be rehospitalized for ACS, and 49% more likely to need a revascularization procedure, compared with patients on clopidogrel only (JAMA 2009;301:937-44). All three increased relative risks were statistically significant.

The results suggest that in such patients prescribed a PPI for prophylaxis or for reflux symptoms, an alternative gastroprotective drug should be considered, such as a histamine H_2-receptor antagonist, sucralfate, or misoprostol, said Dr. Ho, who acknowledged that each of these alternatives may be less effective than a PPI.

Even in high-risk patients with a recent history of a gastrointestinal bleed, "there needs to be an individualized physician and patient decision, weighing the risks and benefits" of taking clopidogrel and a PPI concurrently, Dr. Ho said.

"No one disputes the benefit of a PPI in a patient who has had a bleeding ulcer," Dr. Bhatt noted.

Of the four studies in the past 4 months that examined the interaction between clopidogrel and PPIs, three found a dangerous interaction. The first suggestion of a clinical consequence from concurrent clopidogrel and PPI treatment came in the report at the AHA's scientific sessions last November. Results from a second study reported at the meeting by researchers from the University of Kentucky failed to find evidence of an interaction between clopidogrel and PPIs.

A second report suggesting a dangerous interaction was published online (CMAJ 2009 Jan. 28 [doi:10.1503/cmaj.082001]). The CMAJ report also showed that the increased risk was specific for PPIs that inhibit the p450 2C19 enzyme. Treatment with pantoprazole showed no link with an increased risk for MI rehospitalization.

"If you need to use a PPI, then pantoprazole seems to be a very reasonable strategy," based on both the pharmacology evidence and the "limited but real" clinical evidence in the CMAJ study, Dr. Peterson said.

Dr. Ho and most of his coauthors reported having no financial disclosures. Dr. Peterson reported receiving honoraria and research support from Bristol-Myers Squibb and Sanofi Aventis, the companies that market clopidogrel. ■

Stroke Tied to Withdrawal of Antithrombotic Medication

BY ROBERT FINN

SAN FRANCISCO — As many as 26,500 ischemic strokes occurring in the United States each year may be associated with patient withdrawal from antithrombotic and antiplatelet medications, according to a study presented at the International Stroke Conference.

Among 2,082 patients in the Cincinnati area who had 2,191 ischemic strokes in 2005, 84 (3.8%) of the strokes occurred in patients who had stopped their medications within 60 days. The first 7 days after withdrawal of antiplatelet or antithrombotic medication appeared to be the most dangerous time, Dr. Jordan Bonomo of the University of Cincinnati reported. Some patients had been on more than one medication simultaneously.

A total of 182 strokes occurred in patients who were either on warfarin or recently had stopped taking the drug.

These results 'mandate continued review of guidelines for withdrawal of anticoagulant and antiplatelet medication in the peri-procedural period.'

Of the 58 strokes that occurred in those who went off warfarin, 31 were within 7 days of withdrawal, 12 between 8 and 14 days, 8 between 15 and 30 days, and 7 between 31 and 60 days.

Similarly, 896 patients had been taking aspirin around the time of their stroke. Of these, 44 had discontinued aspirin; 24 of the strokes occurred within 7 days after halting aspirin therapy; 7 occurred between 8 and 14 days, 11 between 15 and 30 days, and 2 between 31 and 60 days.

The investigators found a similar pattern among 228 patients who had been taking clopidogrel around the time of their stroke, 21 of whom had gotten off the drug—10 strokes occurred within 7 days of discontinuation, 4 between 8 and 14 days, 5 between 15 and 30 days, and 2 between 31 and 60 days.

Dr. Bonomo noted that the greater Cincinnati area is demographically similar to the overall U.S. population. Therefore, of the 692,000 ischemic strokes that occur annually in the United States, an estimated 26,500 occur in patients who have withdrawn from antithrombotic or antiplatelet medications within 60 days.

Of the 84 strokes, 54 (64%) occurred in patients whose medication had been withdrawn on the order of their physicians.

In most cases, physicians ordered withdrawal because of an upcoming medical procedure or because of bleeding. Among the withdrawals that occurred when the patient stopped their medication on their own, noncompliance and financial burden were the most common causes.

These results "mandate continued review of guidelines for withdrawal of anticoagulant and antiplatelet medication in the peri-procedural period," Dr. Bonomo said. To investigate these matters further, the National Heart, Lung, and Blood Institute is funding a clinical trial called Effectiveness of Bridging Anticoagulation for Surgery (The BRIDGE Study) that will begin in May 2009.

Dr. Bonomo stated that he had no conflicts of interest to disclose. The study was supported by the National Institute of Neurological Disorders and Stroke. ■