PPIs Can Cause 'Addiction' to Acid Suppression

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — Patients with gastroesophageal reflux disease are very difficult to wean off proton pump inhibitors, and there is evidence that patients essentially become "addicted" to acid suppression, findings of large study suggest.

Dr. Peter Bytzer, of Copenhagen University and Køge (Denmark) Hospital, and Dr. Christina Reimer, also of the university, reported study findings that indicate proton pump inhibitors (PPIs) are nearly impossible to discontinue, even for patients who lack a formal indication for their use.

"We found that discontinuing long-term PPI therapy was possible in only a minority of patients, and that the majority experiencing symptom relapse after discontinuing the drug had no abnormal endoscopic findings," Dr. Reimer said in a poster presentation. "Rapid recurrence of typical reflux symptoms was the main reason for restarting therapy, and 7 days of esomeprazole was helpful, despite the normal endoscopic findings."

Dr. Bytzer and Dr. Reimer conducted a standardized search of patients prescribed PPIs by primary care physicians in the previous 12 months in Denmark. They identified 901 long-term users (at least 120 tablets), of whom 525 had an endoscopically verified diagnosis of esophagitis, Barrett's esophagus, or peptic stricture or had abnormal pH on monitoring and therefore were categorized as having an indication for long-term treatment.

The remaining 376 patients were considered to have an unverified indication for a PPI, and 76 of them agreed to attempt to discontinue the drug. If symptoms recurred within 6 months after PPI withdrawal, patients underwent endoscopy.

Those without abnormal findings were then randomized to 7 days of PPI therapy with esomeprazole 40 mg/day or placebo.

VITALS

Major Finding: Of 76 patients who had unverified indications for a PPI, 11 were able to discontinue therapy without recurrence of symptoms during 6 months of follow-up.

Data Source: A standardized search of patients prescribed PPIs by primary care physicians in the previous 12 months in Denmark.

Disclosures: Dr. Bytzer is a speaker or consultant for AstraZeneca Pharmaceuticals, Nycomed, and Orexo. Dr. Reimer has received grant support from and is a consultant to AstraZeneca Pharmaceuticals.

Of the 76 patients, 53 (63%) had symptom recurrence within the first week of discontinuing the PPI. The main symptoms were heartburn/acid regurgitation (48%) and dyspepsia (42%), Dr. Reimer said.

On endoscopy, 31 (59%) had no abnormal findings.

Only 11 (14%) discontinued therapy without recurrence of symptoms during the 6 months of follow-up.

The 53 patients with recurrence were randomized to a PPI or placebo for 7 days; 80% of those taking esomeprazole had treatment success, compared with 13% receiving placebo.

There is evidence of an increased prevalence in acid-related conditions, more liberal prescribing habits—including empirical PPI therapy for unspecific dyspepsia—and PPI "dependency" as a result of acid rebound that requires more and more suppression, Dr. Bytzer said.

Ironically, studies have suggested that PPIs can actually stimulate acid secretion in healthy volunteers. A 2007 systemic review concluded "there is evidence from uncontrolled trials for an increased capacity to secrete acid in [*Helicobacter pylori*]–negative subjects after 8 weeks of treatment" (Aliment. Pharmacol. Ther. 2007;25:39-46).

"In other words, once you remove the PPI you get an increased capacity to secrete acid. But is this clinically relevant? Will rebound acid hypersecretion lead to acid-related symptoms?" Dr. Bytzer asked.

Apparently, it can. In a blinded withdrawal study conducted by Dr. Bytzer's group, 120 healthy volunteers were randomized to esomeprazole 40 mg or placebo for 8 weeks, after which the esomeprazole group crossed over to placebo for 4 weeks (Gastroenterol. 2009;137:80-7). After crossing over, these patients experienced a significant increase in dyspepsia, heartburn, and regurgitation at weeks 10-12.

"These subjects had not had symptoms prior the study and were never on acid reducers. They were unaware of the shift to placebo. After starting a PPI, gastrin significantly increased, and 44% got significant acid-related symptoms," he reported.

Other investigators have found increases in reflux laryngitis, heartburn, and dyspepsia after discontinuation of PPIs, he added.

Recently, in a double-blind placebo-controlled trial in 48 *H. pylori*–negative volunteers, dyspeptic symptoms developed after discontinuation of pantoprazole (Am. J. Gastroenterol. 2010 March 23; doi:10.1038/ajg.2010.81). A total of 11 out of 25 (44%) subjects in the pantoprazole group developed dyspepsia, compared with 2 out of 23 (9%) in the placebo group. During the first week after discontinuation, the pantoprazole group had a mean symptom score of 5.7 versus 0.74 in the placebo group, but these scores progressively declined over 3 weeks.

"We can conclude that PPI therapy induces acid-related symptoms in around 44% of previously asymptomatic subjects, and this rebound acid hypersecretion is probably clinically relevant," Dr. Bytzer said. "It seems that we may be inducing reflux disease when we give PPIs for non–acid-related symptoms."

When attempting to discontinue PPI therapy in long-term users, patients can slowly taper down doses over 3 weeks or so, he suggested. However, he said it remains difficult to discontinue PPI therapy, especially in patients with GERD. ■

Insulin Resistance May Raise Risk of Barrett's Esophagus

BY HEIDI SPLETE

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — High insulin levels, insulin resistance, and central body fat were each significantly associated with an increased risk of Barrett's esophagus in a recent case-control study.

Previous studies have shown that obesity increases the risk of both esophageal adenocarcinoma and its precursor, Barrett's esophagus (BE). In this study, Dr. Katarina Greer and her colleagues investigated whether central adiposity, hyperinsulinemia, and insulin resistance are independent risk factors for BE.

"The mechanism through which obesity promotes cancer is still largely unknown," said Dr. Greer of University Hospitals Case Medical Center in Cleveland.

The researchers identified 135 adults with BE among consecutive patients seen at a single tertiary care center. The average age of the BE patients was 64 years. These patients were compared with two control groups—135 adults with gastroesophageal reflux disease (GERD) and 932 control adults who were undergoing routine colonoscopies.

Overall, high levels of insulin and insulin resistance were significant independent risk factors for BE, Dr. Greer noted. Individuals in the highest quartile of serum insulin had a 2.8-fold increase in the risk of BE, compared with those in the lowest quartile, when the two control groups were combined in a multivariate analysis controlling for age, sex, and waist-to-hip ratio.

VITALS

Major Finding: Individuals in the highest quartile for serum insulin level were 2.8 times more likely to have Barrett's esophagus, compared with those in the lowest quartile.

Data Source: A case-control study including 135 Barrett's esophagus patients, 135 controls with gastroesophageal reflux disease, and 932 controls undergoing colonoscopies.

Disclosures: Dr. Greer stated that she had no financial conflicts of interest.

Regarding insulin resistance, individuals in the highest quartile of values for the homeostasis model assessment–insulin resistance (HOMA-IR) were about three times more likely to develop BE, compared with those in the lowest quartile.

HOMA-IR was calculated using baseline fasting insulin and glucose levels. Mean fasting insulin levels were significantly higher in BE patients vs. colonoscopy patients (10.1 vs. 7.4 microIU/mL).

In addition, BE patients were more insulin resistant than either of the control groups. The mean HOMA-IR in the BE group was 2.7, compared with 1.8 for the control groups.

The average body mass index was 30.8 kg/m^2 for the BE patients, 29.6 for the GERD patients, and 29.3 for the colonoscopy patients. Central adiposity was assessed based on the waist-to-hip ratio. The mean waist-to-hip ratio was significantly higher in patients with BE, compared with colonoscopy controls (0.98 vs. 0.91, respectively). But there was no significant difference in mean waist-to-hip ratio between BE patients and GERD controls (0.98 vs. 0.97). This suggests that central adiposity may play a role in progression to esophageal cancer, Dr. Greer said.

The findings support existing evidence of a connection between insulin and cancer, but additional studies are needed to examine whether losing weight and treating insulin resistance can disrupt or reverse progression to cancer in BE patients, Dr. Greer said. ■