PPI Withdrawal Triggers Acid Hypersecretion

BY MARY ANN MOON

Ending an 8-week course of a proton pump inhibitor caused rebound heartburn, acid regurgitation, and dyspepsia in healthy volunteers, Dr. Christina Reimer and her colleagues reported.

Rebound symptoms were clinically significant in the study subjects, causing mild to moderate discomfort for at least 2 weeks after withdrawal of daily PPI therapy—a "remarkable" finding given that 40% of the study subjects had never experienced such symptoms before, wrote Dr. Reimer of the department of medical gastroenterology at Copenhagen University and her associates.

Although ongoing PPI therapy is indicated only in patients who have persistent gastroesophageal reflux or who are taking NSAIDs, physicians have long reported that it is difficult to reduce or withdraw the drug after a 4-week or 8-week course of empiric treatment for dyspepsia. This has led some to suspect that perhaps physiologic changes induced by the drug itself cause hypersecretion after the PPI is withdrawn.

To investigate the issue, Dr. Reimer and her colleagues performed a double-blind trial in 120 healthy volunteers who had no acid-related symptoms. Sixty subjects were randomly assigned to receive 40 mg of esomeprazole daily for 8 weeks followed by 4 weeks of identical placebo tablets (withdrawal period), and the other 60 subjects were assigned to 12 weeks of placebo.

All were given antacid tablets to be used as rescue medication if they developed acid-related symptoms during the study.

The study subjects completed weekly electronic questionnaires that included the Gastrointestinal Symptom Rating Scale (GSRS). They also were assessed using the 36-item Short Form Health Survey (SF-36) and gave blood samples so that plasma levels of gastrin and chromogranin A could be tracked as indirect measures of gastric acid suppression and enterochromaffin cell mass.

After active treatment was withdrawn but subjects still thought they were taking the drug, "a significant and increasing difference between the PPI and the placebo group" was seen in dyspepsia and reflux symptom scores. A total of 44% of the PPI group reported heartburn, acid regurgitation, or dyspepsia, compared with only 15% of the placebo group.

The proportion of PPI-treated subjects who reported acid-related symptoms was 22% during the second week after withdrawal, 22% during the third week after withdrawal, and 21% during the fourth week after withdrawal. In contrast, the proportions of placebo subjects who reported such symptoms were 7%, 5%, and 2%, respectively.

The differences between the two groups also were significant for each of the individual components of the acid-related GSRS scores. In contrast, GSRS scores for diarrhea and constipation were not significantly different.

In addition, 52% of the active-treatment group reported using rescue antacids after PPI withdrawal. In contrast, only 11% of the placebo group used rescue antacids.

"Our study results reveal for the first time that profound acid inhibition with a PPI for 8 weeks induces acid-related symptoms in a significant proportion of subjects after withdrawal of therapy," the investigators said.

Moreover, the increased use of rescue antacids after PPI withdrawal "attests to the clinical relevance of the observed symptoms," they added.

Other researchers have investigated whether tapering the use of PPIs might help long-term users discontinue the drugs. In one clinical trial, "tapering over 3 weeks did not have a significant effect on the proportion that successfully withdrew treatment, compared to instant discontinuation," they said.

In their study, subjects continued to report acid-related symptoms 4 weeks after withdrawal, and two other studies of PPI withdrawal showed increased acid secretion at least 8 weeks after PPIs were discontinued. Therefore, the duration of rebound acid hypersecretion remains unknown at present and tapering the medication does not appear to help.

"Our results justify the speculation that PPI dependency could be one of the explanations for the rapidly and continuously increasing use of PPIs," they noted.

AstraZeneca supplied the medication and placebo used in this study. ■

Foodborne Infections May Increase Risk of IBD

BY HEIDI SPLETE

CHICAGO — A history of foodborne infections nearly triples the risk of inflammatory bowel disease, based on data from a population-based study of nearly 40,000 adults.

"We have seen increased incidence of both colitis and Crohn's disease in recent years," said Dr. Henrik Nielsen of Aalborg (Denmark) Hospital. The pathogenesis of inflammatory bowel disease remains uncertain, Dr. Nielsen said at the annual Digestive Disease Week. Previous studies have suggested a role for environmental factors, including infections, but few of these studies have included long-term follow-up data.

Dr. Nielsen and his colleagues used laboratory registries from 1991 to 2003 to identify 13,148 adults with a history of *Salmonella* or *Campylobacter* gastroenteritis, as well as 26,216 controls without a history of these infections. The researchers followed the study population for up to 15 years, with an average follow-up period of 7.5 years.

A first-time diagnosis of inflammatory bowel disease (IBD) during the follow-up period was reported in 107 individuals with a history of *Salmonella* or *Campylobacter* infections, compared with 73 controls. The risk of IBD was independent of age and sex, and it was similar for both pathogens. In the group with the history of infections, the odds ratio for IBD was 2.9 during the entire follow-up period and 1.9 if the first year after infection was excluded.

"We documented both short-term and long-term increased risk of IBD following confirmed infections," Dr. Nielsen said. The study could not prove causality because of its retrospective nature, but the results may contribute to a better understanding of the etiology of IBD as more research is done, he added.

The findings also emphasize the importance of food safety for disease prevention, Dr. Nielsen said at a press conference. The increased volume of imported foods and changes in food production may create more challenges for safe food handling, he said.

Dr. Nielsen had no financial conflicts to disclose. ■

To view a video interview of Dr. Nielsen, go to: www.youtube.com/watch?v=GDVlFRfYojI.

IBD During Pregnancy May Affect Child Health, Development

BY HEIDI SPLETE

CHICAGO — Inflammatory bowel disease during pregnancy has significant short- and long-term effects on children, based on data from 146 women who had IBD for an average of 11 years.

Previous research has described the effects of IBD during pregnancy on perinatal outcomes, but the impact of maternal IBD on child health and development has not been well studied, Dr. Iris Dotan said at the annual Digestive Disease Week.

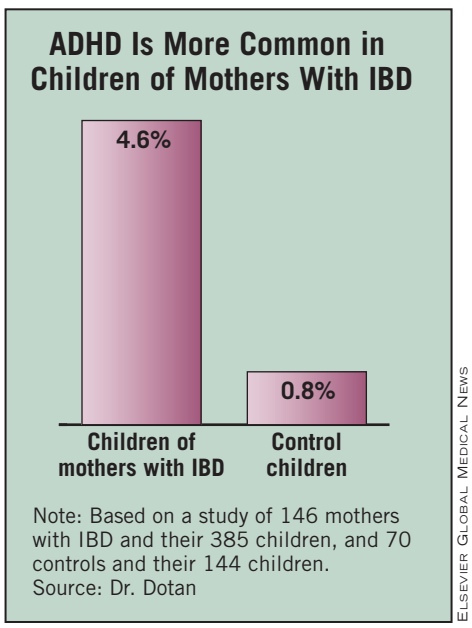
Dr. Dotan and her colleagues at Tel-Aviv Sourasky Medical Center in Gush Dan, Israel, reviewed data from children's medical records and follow-up questionnaires. Their study group included 146 women with IBD (93 with Crohn's disease and 53 with ulcerative colitis) and their 385 children, who were compared with 70 control mothers and their 144 children.

One-third of the women reported IBD exacerbation during pregnancy, and 45% of these exacerbations occurred in the first trimester. Women with IBD were slightly older than the control women (43 years vs. 40 years), and they had significantly more miscarriages than controls (0.68 vs. 0.33).

Overall, the average birth weights were significantly lower in the babies born to IBD mothers vs. controls (3.13 kg vs. 3.27 kg). The trend toward smaller size continued in adolescence. At approximately 14 years of age, the average height and weight of the children born to IBD mothers were significantly less than in control children (1.28 m vs. 1.47 m; 29.3 kg vs. 39.0 kg).

Children of IBD mothers were significantly more likely to have first-year intercurrent infections compared with controls. And 3% of the children of IBD mothers had IBD themselves, which was a significant difference compared with the control children. By contrast, control children had significantly more cases of atopic dermatitis than did children of IBD mothers (11% vs. 5%).

Learning difficulties and attention-deficit/hyperactivity disorder were significantly more common in children born to IBD mothers compared with controls (5% vs. 0.8%; 4.6% vs. 0.8%). Gross neurologic abnormalities were significantly more common in children of IBD mothers compared with controls (4.4% vs. 0.7%). But no significant differences were found in the incidence of autism, dyslexia, or abdominal pain between the two groups of children.



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The study was limited by a lack of information about the effect of disease severity, said Dr. Dotan.

"Large-scale studies are needed to confirm results and assess the role of inflammation," she noted.

Dr. Dotan had no financial conflicts to disclose. ■