GERD

Increased gastric acid secretion as a possible cause of GERD

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Many experts maintain that GERD is caused by dysfunction of the gastroesophageal barrier and that gastric acid secretion is not the primary underlying defect. By contrast, a recent study by Reimer and colleagues raises the possibility that increased gastric acid secretion is an important cause of GERD.

Reimer and colleagues[1] report results from a randomized, double-blind, placebo-controlled study of healthy individuals who received 40 mg daily doses of the PPI esomeprazole or placebo for 8 weeks, followed by placebo for 4 weeks in both groups. Of 59 individuals who received esomeprazole, 26 (44%) experienced at least one episode of clinically significant heartburn, dyspepsia or acid regurgitation during weeks 9–12, in contrast with nine of 59 (15%) individuals who received placebo. At weeks 10, 11 and 12 the percentage of individuals with clinically significant heartburn, dyspepsia or acid regurgitation was 21–22% for the esomeprazole group and 2–7% for the placebo group. Fasting plasma gastrin concentrations at weeks 4 and 8 were significantly higher in the esomeprazole group than in the placebo group, although all values were in the normal range. Increased plasma gastric concentrations in the esomeprazole group returned to baseline after treatment was stopped. Fasting plasma concentrations of chromogranin A, an indirect measure of enterochromaffin cell mass, were significantly higher at weeks 8 and 12 in individuals who received esomeprazole than in those who received placebo.

Reimer and colleagues[1] concluded that their findings of increased gastroesophageal symptoms in patients treated with esomeprazole resulted from rebound hypersecretion of gastric acid that occurred after the PPI treatment was stopped.[2–4] The explanation for rebound acid hypersecretion is that PPIs cause hypergastrinemia, which in turn causes hyperplasia of gastric parietal cells (which secrete acid) and also hyperplasia of enterochromaffin cells (which mediate the action of gastrin on acid secretion by releasing histamine).[2] When PPI treatment is stopped, the increased numbers of parietal and enterochromaffin cells then amplify the effects of normal physiologic stimuli on gastric acid secretion. The results from the study by Reimer and colleagues also support the hypothesis that the symptoms of GERD can be triggered in healthy individuals simply by increasing gastric acid secretion.

Many experts maintain that GERD is caused by dysfunction of the gastroesophageal barrier and that gastric acid secretion is not the primary underlying defect.[2] A few studies have, however, raised the possibility of a link between increased gastric acid secretion and GERD,[2] but the importance of these findings has been difficult to determine and they have been largely ignored. Although one study reported that basal or pentagastrin-stimulated gastric acid secretion in esophagitis was comparable to that in unspecified medical conditions without esophagitis,[5] other studies have reported increased basal, peak or maximal gastric acid secretion in patients with GERD compared with that in healthy individuals.[6–8] Meal-stimulated gastric acid secretion and postprandial gastric acidity were also found to be significantly increased in patients with GERD compared with in healthy controls.[9]

Reimer and colleagues proposed that since not all individuals experienced acid-related symptoms after esomeprazole treatment, rebound acid hypersecretion, which might have been experienced by all treated individuals, might only trigger clinically relevant symptoms in those with pre-existing lower esophageal sphincter dysfunction and a predisposition to reflux. An equally likely explanation is that only a fraction of individuals experienced rebound acid hypersecretion.[1]

Without knowing the likelihood that stopping the PPI would lead to increased symptoms of GERD, Reimer *et al.*, understandably, did not measure 24 h gastric and esophageal pH at baseline and after withdrawal of the PPI to confirm increased gastric acidity and increased esophageal acid exposure. Interpretation of the authors' findings, therefore, depends critically on two important studies that assessed changes in basal and gastrin-stimulated gastric acid secretion in healthy individuals before and after 8 weeks of daily treatment with 40 mg omeprazole, another PPI.[3,4] Evidence for rebound hypersecretion of gastric acid from these studies was not strong[10] and although both studies showed a significant increase in gastrin-stimulated gastric acid output, only one[8] showed a significant increase in basal acid output after omeprazole treatment.

That study provided values for basal and gastrin-stimulated gastric acid output in 12 and 11 individuals, respectively (Figure 1; even though the authors report that 12 individuals were studied for gastrin-stimulated acid output, I could only find data for 11 individuals in Figure 2 of their article).[8] 15 days after the 8-week treatment course with the PPI had been stopped, 10 individuals showed an increase and two showed a decrease in basal gastric acid output (Figure 1a), while 10 individuals showed an increase and one showed a decrease in gastrin-stimulated gastric acid output (Figure 1b). The study did not include a control group of individuals receiving placebo. If it had, one would expect that half of the participants, on average, would have higher gastric acid output and half would have lower output than their corresponding baseline output. In that case, the differences in gastric acid output between

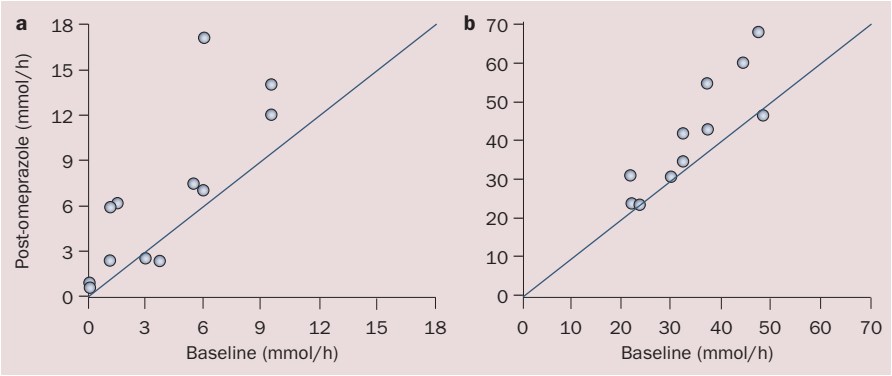

Figure 1 | Gastric acid output measured at baseline and 15 days after stopping 8 weeks of treatment with omeprazole in healthy individuals not infected with *Helicobacter pylori*. Points above the diagonal line (identity line) indicate that the value after omeprazole treatment is higher than the corresponding baseline value and points below the identity line indicate the opposite. The magnitude of the difference between post-omeprazole and baseline values is given by either the vertical or the horizontal distance between the point and the identity line. **a** | Basal gastric acid output, 12 individuals. **b** | Gastrin-stimulated gastric acid output, 11 individuals. Values were estimated from Figures 1 and 2 in Gillen *et al.*[3]

individuals treated with omeprazole and controls would not be significant because of the small sample size ($P = 0.19$ and $P = 0.07$, calculated by Fisher's Exact Test, for basal and gastrin-stimulated gastric acid output measurements, respectively). Assuming that half of the individuals receiving placebo would show an increase in basal acid output and in gastrin-stimulated acid output after the placebo was stopped, a sample size of 40 in each group would be required to have 90% power to detect the increase in basal acid output illustrated in Figure 1a with a significance level of 0.05. Similarly, a sample size of 25 in each group would be required to have 90% power to detect the increase in gastrin-stimulated acid output illustrated in Figure 1b with a significance level of 0.05.

Furthermore, I find it improbable that the six points closest to the identity line in Figure 1a or the five points closest to the identity line in Figure 1b represent clinically important changes in gastric acid output that would be likely to induce symptoms of GERD. Thus, the analysis of these results suggests that only a fraction of the individuals treated with the PPI in the study of Reimer and colleagues manifested acid-related symptoms because they were the only participants that developed a sufficiently high rebound gastric acid hypersecretion to lead to an increase in esophageal acid exposure.

The studies that have reported PPI-induced rebound gastric acid hypersecretion have lacked appropriate control groups.[10] The study by Reimer and colleagues[1] addressed this shortcoming by measuring gastroesophageal symptoms in healthy human individuals following withdrawal of treatment with either a PPI or placebo. The authors found that the prevalence of clinically relevant heartburn, dyspepsia or acid regurgitation was significantly higher after stopping the PPI than after stopping placebo. These findings raise the possibility that increased gastric acid secretion is a primary pathologic abnormality in GERD. Future studies should try to measure symptoms, gastric pH and esophageal pH to expand on the very important findings by Reimer *et al.*

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Competing interests
The author declares an association with the following company: Science for Organizations. See the article online for full details of the relationship.

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CROHN'S DISEASE

Bacterial clearance in Crohn's disease pathogenesis

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Evidence from a recent study strongly implicates innate immunity in the etiology of Crohn's disease, with particular focus on impaired secretion of cytokines and chemokines by intestinal macrophages in response to bacterial stimuli. These findings highlight the importance of acute inflammatory responses in the first stages of disease pathogenesis.

Crohn's disease is a chronic form of IBD that affects one in 1,000 adults. Owing to its complex etiology, the mechanisms underlying the initial manifestation of disease have not been entirely elucidated. The characteristic inflammatory symptoms are, however, known to arise from defects in the epithelial barrier and the mucosal immune