

Evidence That Proton-Pump Inhibitor Therapy Induces the Symptoms it Is Used to Treat

See “Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy,” by Reimer C, Søndergaard B, Hilsted L, et al, on page 80.

Since their clinical launch 25 years ago, the use of proton-pump inhibitors has increased progressively with approximately 5% of the developed world now receiving such treatment.^{1,2} Several factors are likely to be contributing to the increase in usage of proton-pump inhibitors, but in this month’s *GASTROENTEROLOGY* Reimer et al³ suggest that the drugs themselves may be causing or aggravating the disease process they are used to treat. Forty-four percent of previously asymptomatic subjects experienced clinically significant heartburn, acid reflux, or dyspepsia after discontinuing a 2-month course of esomeprazole 40 mg/d compared with 15% after placebo. The authors propose that this is a clinical manifestation of the rebound acid hypersecretion arising from the trophic effects of the proton-pump inhibitor-induced hypergastrinemia on the oxyntic mucosa.

Owing to their substantial elevation of intragastric pH, proton-pump inhibitor therapy produces a substantial increase in the circulating gastrin concentration.⁴ Gastrin activates the cholecystokinin-2 receptor on the enterochromaffin-like cells, causing them to release histamine, which then acts on the H₂ receptor of the parietal cell, thereby stimulating acid secretion. However, gastrin also exerts a powerful trophic effect on the enterochromaffin-like cells and the parietal cells of the oxyntic mucosa (Figure 1).⁵⁻⁷ The marked trophic effects of proton-pump inhibitor-induced hypergastrinemia caused major concerns during early animal safety tests as a proportion of female rats on long-term omeprazole developed carcinoid tumors of their oxyntic mucosa.⁷

In humans, proton-pump inhibitor-induced hypergastrinemia produces functional, as well as hyperplastic morphologic changes, of the oxyntic mucosa. In 1996, Waldum et al⁸ reported that at 14 days after discontinuation of a 3-month course of omeprazole 40 mg/d, gastric acid secretory capacity was increased by 50%.⁸ Our own group demonstrated that the phenomenon also occurred after 2 months treatment and was confined to *Helicobacter pylori*-negative subjects.⁹ This increased acid-secreting capacity persists for ≥2 months.¹⁰ The absence

of the phenomenon in *H pylori*-infected subjects is probably due to the marked exacerbation of the gastritis of the oxyntic mucosa induced by proton-pump inhibitor therapy in such subjects, reducing its sensitivity to gastrin stimulation.

In their study in this issue of *GASTROENTEROLOGY*, Reimer et al³ investigated whether this rebound acid hypersecretion is of clinical significance. One hundred twenty subjects without any clinically significant history of reflux symptoms were randomized in double-blind fashion to 2 months treatment with esomeprazole 40 mg/d or placebo and then during the subsequent 4 weeks all received placebo. During weeks 2, 3, and 4 posttreatment, clinically significant symptoms of heartburn, acid reflux, or dyspepsia were reported by 44% of those who had received omeprazole versus only 15% of those who had received placebo throughout ($P < .001$). The duration of these rebound symptoms is unclear because they were still present at the end of the monitoring period 4 weeks after discontinuing the treatment.

In patients without peptic ulcer disease, acid-related symptoms usually arise from noxious effects of acid on the esophageal squamous mucosa. A degree of gastroesophageal reflux is common in asymptomatic subjects

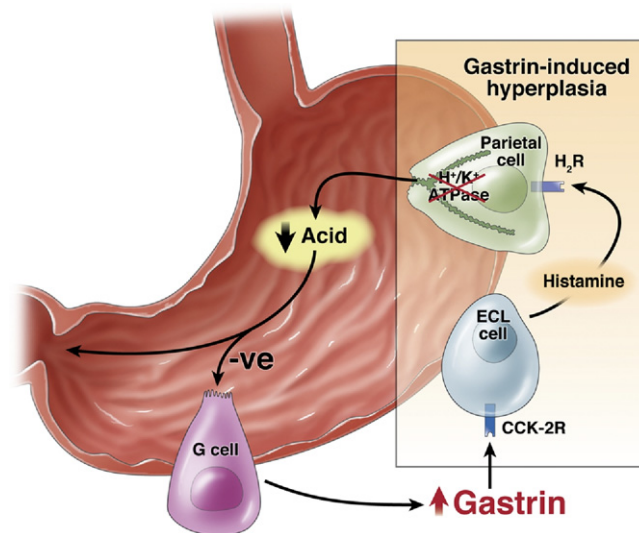


Figure 1. The increased gastrin concentration during proton-pump inhibitor therapy exerts trophic effects on the oxyntic mucosa causing hyperplasia and increased functional capacity of the enterochromaffin-like (ECL) cell and parietal cell. As a consequence, on discontinuing the proton-pump inhibitor there is rebound acid hypersecretion which persists for at least 2 months.

and rebound hyperacidity increases the acidity and volume of the refluxate and thus its ability to induce damage and symptoms.^{4,9,10} The timing of onset of the symptoms at 1 week after discontinuing the proton-pump inhibitor and continuing for at least 4 weeks corresponds very closely with the pattern of acid hypersecretion demonstrated after such treatment.^{4,8-11} It is also possible that the marked suppression of intragastric acidity during proton-pump inhibitor therapy may down-regulate some of the mechanisms known to protect the esophagus from acid exposure or up-regulate mechanisms involved in perception of esophageal acid exposure.

What are the clinical implications of this observation? Proton-pump inhibitor therapy is now being prescribed for a wide variety of upper gastrointestinal symptoms on the basis that they might be acid induced and therefore may benefit from such treatment.^{1,2} This increasingly liberal usage of these powerful drugs is due to a number of factors, including reduced concerns about potential side effects, reduced cost, and the lack of alternative therapies for upper gastrointestinal symptoms. This liberal employment of proton-pump inhibitor therapy has been recommended recently by many national and international guidelines based on “number needed to treat” and health economic analyses.^{12,13} As a consequence, a substantial proportion, if not majority, of patients now prescribed proton-pump inhibitor therapy do not have acid-related symptoms and therefore have no true indication for such therapy. The current finding that these drugs induce symptoms means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment. It is likely also that treatment of mild reflux symptoms with such therapy may aggravate the underlying disease and lead to an increased requirement for long-term therapy. Studies are required to investigate whether early treatment of mild reflux disease with proton-pump inhibitor therapy results in aggravation of the natural history of the condition.

This important study by Reimer et al³ certainly challenges current liberal proton-pump inhibitor prescribing habits. A number of changes in prescribing habits need to be considered, including the following.

1. Efforts should be pursued to try to restrict proton-pump inhibitor therapy use to those likely to derive benefit. Clearly, subjects with symptoms accompanied by endoscopic evidence of erosive esophagitis or of increased esophageal acid exposure merit treatment. If proton-pump inhibitor therapy is being considered for symptoms in patients who have not been investigated, then it should be reserved for those with clear symptoms of heartburn or acid reflux. It should be emphasized that there is very little evidence of symptomatic benefit from proton-pump inhibitor therapy in patients with epigastric discomfort that is not attributable to underlying peptic ulcer disease.¹⁴
2. When using proton-pump inhibitor therapy as a diagnostic test for possible acid-related symptoms, it seems to be appropriate to implement a short course (1–2 weeks) to reduce the chance of inducing hyperacidity and associated symptoms. Further studies are required to clarify the influence of dosage and duration of treatment on both rebound acid hypersecretion and rebound symptoms.
3. The current study also challenges the increasing tendency to adopt a “step-down” rather than “step-up” approach to the treatment of patients presenting with symptoms assumed to be from acid reflux. More effort should be made to identify contributory lifestyle factors and to utilize milder medications such as antacids or alginates. Unfortunately, H₂ receptor antagonists also induce rebound acid hypersecretion and induce rebound symptoms in previously asymptomatic subjects, although the duration of these is shorter than that reported after proton-pump inhibitor treatment.¹⁵⁻¹⁷
4. Patients often ask about the safety and likelihood of side effects from proton-pump inhibitory therapy. Now that rebound acid secretion has been demonstrated to induce symptoms, we are probably obliged to inform them about rebound acid hypersecretion and its potential effects.

This study by Reimer et al³ also highlights the fact that gastrin-induced hyperplasia is a clinically relevant inherent weakness in the mechanism of action of proton-pump inhibitor therapy. Although highly effective at controlling acid-related disease during therapy, the drugs may exacerbate the underlying disease process that becomes manifest upon discontinuation of the treatment. It would be better to have a drug that controlled acid and acid-related symptoms during treatment and left them no worse or even better after stopping the treatment. Gastrin receptor antagonists inhibit acid secretion, and by blocking the trophic effect of gastrin, may also reduce the stomach's acid secretory capacity.¹⁸ However, use of such agents may have limited efficacy as monotherapies because their acid inhibitory potency is less than proton-pump inhibitors.¹⁹ In animals, a combination of a proton-pump inhibitor plus a gastrin receptor antagonist has been demonstrated to effectively prevent rebound acid hypersecretion.²⁰ Perhaps the demonstration of the clinical importance of rebound acid hypersecretion will rekindle interest in such treatment.

Treating gastroesophageal reflux disease with profound acid inhibition will never be ideal because acid secretion is not the primary underlying defect. Acid secretion is normal in most patients with reflux disease and

acid inhibitory therapy makes it abnormally low. It is never ideal to treat 1 abnormality by creating another, as was the case for many years with management of ulcer disease before the discovery of *H pylori* infection. The pathophysiology of acid reflux concerns the dysfunction of the gastroesophageal barrier and research needs to refocus on ways of restoring its competence rather than merely suppressing gastric acid secretion.

KENNETH E. L. MCCOLL

DEREK GILLEN

*Division of Cardiovascular & Medical Sciences
University of Glasgow
Gardiner Institute
Glasgow, UK*

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Reprint requests

Address requests for reprints to: Kenneth E. L. McColl, MD, Division of Cardiovascular & Medical Sciences, University of Glasgow, Gardiner Institute, 44 Church Street, Glasgow, G11 6NT, UK. e-mail: k.e.l.mccoll@clinmed.gla.ac.uk.

Conflicts of interest

The authors disclose no conflicts.

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