# CLINICAL—ALIMENTARY TRACT

## Proton-Pump Inhibitor Therapy Induces Acid-Related Symptoms in Healthy Volunteers After Withdrawal of Therapy

CHRISTINA REIMER,* BO SØNDERGAARD,* LINDA HILSTED,[‡] and PETER BYTZER*

*Department of Medical Gastroenterology, Køge University Hospital, Copenhagen University; and the [‡]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark

**BACKGROUND & AIMS:** Rebound acid hypersecretion (RAHS) has been demonstrated after 8 weeks of treatment with a proton-pump inhibitor (PPI). If RAHS induces acid-related symptoms, this might lead to PPI dependency and thus have important implications. **METHODS:** A randomized, double-blind, placebo-controlled trial with 120 healthy volunteers was conducted. Participants were randomized to 12 weeks of placebo or 8 weeks of esomeprazole 40 mg/d followed by 4 weeks with placebo. The Gastrointestinal Symptom Rating Scale (GSRS) was filled out weekly. A score of $>2$ on 1 of the questions regarding heartburn, acid regurgitation, or dyspepsia was defined as a clinically relevant acid-related symptom. **RESULTS:** There were no significant differences between groups in GSRS scores at baseline. GSRS scores for acid-related symptoms were significantly higher in the PPI group at week 10 ($1.4 \pm 1.4$ vs $1.2 \pm 0.9$; $P = .023$), week 11 ($1.4 \pm 1.4$ vs $1.2 \pm 0.9$; $P = .009$), and week 12 ($1.3 \pm 1.2$ vs $1.0 \pm 0.3$; $P = .001$). Forty-four percent (26/59) of those randomized to PPI reported $\geq 1$ relevant, acid-related symptom in weeks 9–12 compared with 15% (9/59; $P < .001$) in the placebo group. The proportion reporting dyspepsia, heartburn, or acid regurgitation in the PPI group was 13 of 59 (22%) at week 10, 13 of 59 (22%) at week 11, and 12 of 58 (21%) at week 12. Corresponding figures in the placebo group were 7% at week 10 ($P = .034$), 5% at week 11 ($P = .013$), and 2% at week 12 ($P = .001$). **CONCLUSIONS: PPI therapy for 8 weeks induces acid-related symptoms in healthy volunteers after withdrawal. This study indicates unrecognized aspects of PPI withdrawal and supports the hypothesis that RAHS has clinical implications.**

The use of proton-pump inhibitors (PPIs) for acid-related symptoms and disorders is extensive and rapidly escalating. In Denmark, the total use of PPIs increased 7-fold from 1993 to 2007. Even in the last 5 years (2003–2007), the use increased substantially from 20 to 33 defined daily doses per 1,000 persons per day. In 2006, approximately 7% of the Danish population was treated with a PPI.[1] Although the incidence of new treatments with PPIs remains stable, the prevalence of long-term treatment is rising.[2] The reasons for the increasing long-term use are not fully understood.

Treatment with PPIs is initiated mainly by primary care physicians, usually as empirical therapy for dyspeptic symptoms. Empirical PPI therapy for $\geq 4$ weeks in patients with uninvestigated dyspepsia is supported by dyspepsia guidelines.[3,4] Continuous PPI therapy is indicated in cases of severe gastroesophageal reflux disease or as prophylactic therapy for patients who must continue treatment with nonsteroidal anti-inflammatory drugs.[5] However, studies have shown that up to 33% of patients who initiate PPI treatment redeem repeated prescriptions without an obvious indication for maintenance therapy.[6,7] Moreover, studies have shown that primary care physicians perceive withdrawal or reduction of long-term PPI treatment as difficult to achieve.[8,9] Recurrence of symptoms of underlying acid-related disease is an obvious explanation for reuptake of PPI therapy, but physiologic changes triggered by the PPI treatment itself, which set off once therapy is withdrawn, could hypothetically lead to aggravation of symptoms or maybe even to new onset of acid-related symptoms. This latter hypothesis is supported by physiologic studies that have implied that treatment with a PPI for $\geq 8$ weeks leads to a temporarily increased capacity to secrete acid after discontinuation of treatment in particular in *Helicobacter pylori*-negative individuals.[10–12] Rebound acid hypersecretion (RAHS), defined as an increase in gastric acid secretion above pretreatment levels after antisecretory therapy,[13] is observed within 2 weeks after withdrawal of treatment and could theoretically lead to acid-related symptoms such as heartburn, acid regurgitation, or dyspepsia that

might result in resumption of therapy. A plausible physiologic theory for the rebound phenomenon suggests that long-term, elevated gastric pH caused by blockage of the proton-pumps stimulates compensatory gastrin release. This in turn induces a hypersecretory state or hypertrophy of the enterochromaffin-like cells, reflected by an increased level of chromogranin A (CgA), which results in an increased capacity to stimulate gastric acid secretion that sets off once PPI therapy is withdrawn.[11,14–16] It is, however, undetermined whether increased acid secretion is of clinical relevance and leads to acid-related symptoms.

We sought to determine the clinical relevance of RAHS to establish whether long-term treatment with a PPI creates a need for continuous treatment. This could add to the increasing long-term use of PPIs and have substantial economic and clinical implications.

## Methods

### Participants

A randomized, double-blind, placebo-controlled trial was conducted between September 2007 and March 2008 at Køge University Hospital, Denmark. Healthy volunteers without acid-related disease or symptoms were chosen as our study population to establish that the symptoms observed were actually symptoms caused by the acid rebound phenomenon and not relapse of symptoms of underlying disease after discontinuation of treatment.

We advertised for healthy volunteers in student papers, on a student web site, and among hospital staff. Participants were ineligible if they had suffered from dyspepsia, heartburn, or acid regurgitation 4 weeks before enrolment had previously used $H_2$-blockers or PPIs, had any previous contact with health care professionals because of dyspepsia or reflux symptoms, had previous surgery in the upper abdomen, or used nonsteroidal anti-inflammatory drugs, antacids, antidepressants, or analgesics regularly. Participants were asked specifically if they had ever experienced isolated episodes of heartburn, acid regurgitation, and dyspepsia, and were excluded if they had been bothered from these symptoms regularly.

A total of 120 participants >18 years of age were enrolled after providing written, informed consent. The study was monitored according to GCP guidelines by the GCP-Unit, Copenhagen University, Denmark, and approved by The Regional Ethics Committee, Region Sjaelland, Denmark (SJ-8). The study is registered with ClinicalTrials.gov (number NCT00526006).

### Procedures

The randomization list was generated by the drug manufacturer and subjects were randomly assigned consecutively to 1 of 2 treatment arms using sealed envelopes. Each code in the envelope matched the numbered study drug containers. The placebo and active drug were identical in appearance.

Sixty volunteers were allocated to 40 mg of esomeprazole once daily for 8 weeks followed by 4 weeks of identical placebo tablets and 60 volunteers were allocated to 12 weeks of placebo once daily. The study drug was distributed for self-administration for 4 weeks at a time at baseline and at follow-up visits in weeks 4 and 8. Participants were informed that they would either receive placebo for the entire 12-week study period or PPI (esomeprazole) in 1 and placebo in another phase of the study. To ensure complete masking of the volunteers, no information on the length of the period with possible PPI treatment was provided. At baseline, antacid tablets were distributed for use in case of bothersome, acid-related symptoms during the study. Remaining antacids were returned and counted at the final visit in week 12.

Participants were followed with outpatient visits at baseline (week 0) and weeks 4, 8, and 12 and were financially compensated (DKK 4000, €530, $830) for their participation at the visit in week 12.

At baseline, a urea breath test with measurement of exhaled $^{13}CO_2$ before and 30 minutes after ingestion of 75 mg $^{13}$C-marked urea was performed to determine *H pylori* status. Delta over baseline >4% was considered positive. The participants were not informed about the result of the urea breath test until the final visit in week 12. At follow-up visits, participants returned the remaining study drug, which was counted to ensure compliance.

### Symptom Assessments

All questionnaires were completed electronically over the Internet. Once a week, all participants received an e-mail which linked to the relevant questionnaires in an on-line survey tool (SurveyXact, Rambøll Management, Aarhus, Denmark). No missing answers were allowed. Once the questionnaires were filled out and approved by the participants, changes were not possible. To ensure precise monitoring of the development of potential symptoms, all questionnaires had to be filled out within 24 hours.

**Gastrointestinal Symptom Rating Scale.** Participants completed the disease-specific Gastrointestinal Symptom Rating Scale (GSRS) once a week on the same weekday throughout the study starting at baseline (week 0). The GSRS is a 15-item instrument combined into 5 symptom clusters depicting Reflux, Abdominal pain, Indigestion, Diarrhea, and Constipation. The GSRS uses a 7-point, Likert-type scale with 1 representing absence of bothersome symptoms and 7 representing very bothersome symptoms. The scores are calculated by taking the mean of the items completed within an individual scale. Respondents rate the severity of symptoms over the past week. The reliability and validity of the GSRS are well-documented for use in measuring a range of gastrointes-

tinal symptoms and disorders including gastroesophageal reflux disease and dyspepsia.[17–19]

To evaluate the clinical significance of the acid rebound phenomenon a cutoff score of >2 on 1 of the questions on dyspepsia, heartburn, or acid regurgitation corresponding to symptoms causing mild to severe discomfort was chosen as a threshold for characterizing an acid-related symptom as clinically relevant. Respondents who scored ≥2 on 1 of the symptoms on dyspepsia, heartburn, or acid regurgitation were asked additional questions on duration and severity of symptoms with response options mild (1), moderate (2), severe (3), or very severe (4).

At baseline, a score of ≤2 for each of these 3 questions was required to participate in the study to ensure absence of acid-related symptoms in the week before enrolment.

**Short-Form Health Survey.** Participants completed the 36-item Short-Form Health Survey (SF-36) at baseline and at week 12. The SF-36 is a generic instrument that measures functioning and health status in the previous 4 weeks. The SF-36 is extensively used and well-documented in terms of reliability and validity.[20]

**Gastrin and chromogranin A.** As indirect measures of gastric acid suppression and enterochromaffin cell mass, fasting blood samples for measurement of plasma levels of gastrin and CgA were taken at weeks 0, 4, 8, and 12. The samples were immediately centrifuged and the plasma samples were stored at −20°C for further analysis. CgA was measured using the "CgA(340→)" assay.[21] This assay was previously developed in our laboratory, and is specific for the CgA (340–348) sequence of human CgA. P-gastrin was measured by radioimmunoassay using ab.2604, which recognizes the amidated C-terminus of bioactive gastrins.[22]

### Statistical Analysis

Our primary outcome measure was the difference in the combined scores for the GSRS questions: "Have you been bothered by ache or pain in the upper abdomen or behind the breastbone during the past week?" "Have you been bothered by heartburn during the past week?" and "Have you been bothered by acid reflux during the past week?" between the PPI and the placebo group after withdrawal of active treatment in weeks 9–12. With a total of 120 subjects (60 in each arm), a type I error of <5% and a power of 90%, the minimal detectable difference between overall mean in the combined score in weeks 9–12 between the 2 groups was 0.14.

As a secondary outcome measure, we tested the difference in the proportion of subjects with score >2 in 1 of the questions on dyspepsia, heartburn, or acid regurgitation in weeks 9–12. With a sample size of 120 subjects and a type 1 error of <5%, the study had a power of 80% to detect a difference of ≥20% in the proportion of subjects with a score >2 in the GSRS reflux syndrome

scale and question on dyspepsia after withdrawal of treatment.

Other preplanned measures were difference in SF-36 score at week 12 between the 2 groups, difference in total GSRS score, and difference in use of antacids between the groups.

Differences in proportions with clinically significant dyspepsia, heartburn, or acid regurgitation after withdrawal of PPI (weeks 9–12) were assessed with the Fisher exact test. GSRS scores are shown as mean values with standard deviations. Because the scores were not normally distributed, differences were analyzed nonparametrically with the Mann–Whitney test. To take into account the serial and correlated aspect of the GSRS measurements, data were also analyzed by summary measures, which were compared nonparametrically for statistically significant differences between the groups. Overall mean GSRS score in the reflux syndrome scale and overall mean GSRS score in the combined dyspepsia and reflux syndrome scale score in the weeks after withdrawal (weeks 9–12) were chosen as appropriate summary measures.

Multivariate logistic regression analysis with calculation of odds ratios was performed to evaluate independent risk factors for development of clinically significant heartburn, acid regurgitation, or dyspepsia in the actively treated group. Factors included were age, gender, body mass index, smoking, alcohol, *H pylori* status, and any heartburn, acid regurgitation, or dyspepsia ever. Relations between P-gastrin, P-CgA, and symptom scores were evaluated by calculation of the Spearman rank correlation coefficient.

We calculated 95% confidence intervals (CI) to describe the uncertainty of all estimates. For all comparisons, 2-sided *P*-values were calculated; *P* < .05 considered significant. All data analyses were done using SPSS version 15.0.

## Results

Supplementary Figure 1 shows the trial profile. Table 1 shows study participants' baseline demographic and other characteristics. The PPI group was comparable to the placebo group in terms of age, gender, body mass index, smoking, alcohol habits, GSRS and SF-36 scores, previous acid-related symptoms ever, P-gastrin, and P-CgA levels. A significantly higher proportion or participants (13% vs 2%; *P* = .02) in the placebo group was *H pylori* positive.

Compliance, defined as intake of >90% of distributed study drug, was obtained for all 118 volunteers who completed the study.

A significant and increasing difference between the PPI and the placebo group in combined GSRS dyspepsia and reflux syndrome scale score as well as in isolated GSRS reflux syndrome scale score was observed after withdrawal of treatment from weeks 10–12 (Table 2). There

**Table 1.** Baseline Characteristics of Study Subjects

| Characteristics | Esomeprazole (n = 59) | Placebo (n = 60) |
|---|---|---|
| Age, y (range) | 24 (18–45) | 25 (19–58) |
| Women, n (%) | 36 (61) | 34 (57) |
| Body mass index, kg/m$^2$ (range) | 22.5 (16.3–28.8) | 23.7 (16.6–30.8) |
| Smoking, n (%) | 10 (17) | 9 (15) |
| >14/21 units of alcohol/week, n (%) | 3 (5) | 1 (2) |
| Isolated episodes of acid-related symptoms, n (%) | 52/59 (88) | 52/60 (87) |
| Heartburn | 26/59 (44) | 26/60 (43) |
| Acid regurgitation | 49/59 (83) | 42/60 (70) |
| Dyspepsia | 49/59 (83) | 42/60 (71) |
| H pylori infection (urea breath test positive), n (%) | 1 (2) | 8 (13) |
| GSRS scores | | |
| Total | 17.1 (16.4–17.7) | 17.3 (16.6–18.0) |
| Combined for acid-related symptoms[a] | 1.04 (1.0–1.1) | 1.03 (1.0–1.1) |
| GSRS reflux syndrome scale score[b] | 1.04 (1.0–1.1) | 1.03 (1.0–1.06) |
| P-Gastrin, pmol/l (range) | 6.1 (5.1–7.1) | 7.5 (6.2–8.8) |
| P-CgA, pmol/l (range) | 61.7 (49.5–74.0) | 50.1 (43.9–56.2) |

[a]Mean combined score in the 3 GSRS questions on dyspepsia, heartburn, and acid regurgitation.
[b]Mean score in the 2 GSRS questions on heartburn and acid regurgitation.

were no differences at any time point in the proportion of subjects reporting scores >2 for any symptom in the GSRS indigestion, constipation, or diarrhea syndromes.

In weeks 9–12, the overall mean combined GSRS dyspepsia and reflux syndrome scale score in the esomeprazole group was 1.35 compared with 1.12 in the placebo group (P = .001). The overall mean in isolated reflux syndrome scale score was significantly higher in the actively treated group compared with the placebo group (1.36 vs 1.13; P = .009).

A cumulative total of 26 of 59 participants (44%) in the PPI group reported heartburn, acid regurgitation, or dyspepsia during ≥1 of weeks 9–12 compared with only 9 of 59 (15%) in the placebo group (difference 29%; 95% CI, 15.2–47.4%; P < .001). During weeks 10, 11, and 12 (after

withdrawal of PPI) the proportion reporting dyspepsia, heartburn, or acid regurgitation was significantly higher in the PPI group than in the placebo group (Table 3). No statistically significant difference in this proportion between the groups was observed during weeks 0–9. The temporal changes in the proportion in both groups throughout the entire study period are shown in Figure 1. In the subgroup of 26 PPI-treated subjects who had acid-related symptoms during weeks 9–12, use of antacids was reported by 14 of 26 (52%) compared with only 1 of 9 (11%) of the subjects in the placebo group, who reported symptoms (difference 41%; 95% CI, 36.8–77.8%; P = .05). Use of antacids over the entire study period was not more frequently reported in the PPI group compared with the placebo group.

We also compared the reporting of individual symptoms. In week 12, significantly more subjects in the PPI group reported heartburn (difference 12.1%; 95% CI, 3.6–20.5%; P = .006), acid regurgitation (difference 10.3%; 95% CI, 2.4–18.3%; P = .013), and dyspepsia (difference 12.1%; 95% CI, 2.4–21.8%; P = .017) compared with placebo-treated subjects. All other differences for individual symptoms for weeks 9, 10, and 11 were nonsignificant.

A total of 71 ratings of dyspepsia, heartburn, or acid regurgitation were reported by 26 PPI-treated subjects during the 4 weeks after cessation of treatment. Of the 71 ratings, the most frequently reported symptom quality was heartburn (45%) followed by dyspepsia (30%) and acid regurgitation (25%). Out of the 26 subjects with ≥1 report of dyspepsia, heartburn, or acid regurgitation in weeks 9–12, dyspepsia was reported by 11 of 26 (42%) and heartburn or acid regurgitation by 20 of 26 (77%). The mean score for the 71 ratings of the 3 acid-related symptoms in the actively treated group was 3.5 for each of the different symptoms, corresponding with mild to moderate discomfort.

Dyspepsia, heartburn, or acid regurgitation was reported for the first time in week 9 by 9 of the 26 participants, in week 10 by 7, in week 11 by 5, and in week 12 by 5. The median number of weeks with symptoms in ≥1 of the 3 items was 1 (range, 1–4) and mean number of days with symptoms was 4.7 (range, 1–18). The mean

**Table 2.** Cross-Sectional Comparisons of Combined Score in the 3 GSRS Questions on Heartburn, Acid Regurgitation, and Dyspepsia and Score in Isolated GSRS Reflux Syndrome Scale Score in the PPI and Placebo Groups

| Week | PPI mean (SD) | Placebo mean (SD) | Difference (95% CI) | P | PPI mean (SD) | Placebo mean (SD) | Difference (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| 0 | 1.04 (0.13) | 1.03 (0.11) | 0.01 (−0.03 to 0.06) | .35 | 1.04 (0.14) | 1.03 (0.11) | 0.01 (−0.03 to 0.06) | .45 |
| 8 | 1.09 (0.26) | 1.09 (0.28) | 0.00 (−0.10 to 0.10) | .69 | 1.05 (0.20) | 1.10 (0.31) | 0.05 (−0.14 to 0.05) | .45 |
| 9 | 1.29 (0.46) | 1.16 (0.36) | 0.13 (−0.03 to 0.27) | .11 | 1.30 (0.57) | 1.20 (0.45) | 0.10 (−0.08 to 0.29) | .33 |
| 10 | 1.39 (0.72) | 1.16 (0.47) | 0.23 (0.01–0.45) | .02 | 1.38 (0.75) | 1.14 (0.45) | 0.24 (0.01–0.46) | .03 |
| 11 | 1.39 (0.69) | 1.15 (0.48) | 0.24 (0.03–0.46) | <.01 | 1.46 (0.83) | 1.17 (0.52) | 0.29 (0.04–0.54) | .01 |
| 12 | 1.34 (0.62) | 1.04 (0.14) | 0.30 (0.14–0.47) | <.01 | 1.32 (0.70) | 1.04 (0.13) | 0.28 (0.10–0.47) | <.01 |

NOTE. Mean combined score (dyspepsia, heartburn, regurgitation) and mean reflux syndrome scale score (heartburn, regurgitation).

**Table 3.** Comparison of Proportion With Heartburn, Acid Regurgitation, or Dyspepsia

| Week | PPI ($n = 59$) | Placebo ($n = 59$) | Difference in proportion (95% CI) | $P$ |
|------|------|------|------|------|
| 0 | 0% (0/59) | 0% (0/60) | | |
| 8 | 3.4% (2/59) | 3.5% (2/57) | −0.1% (−7.0% to 6.7%) | >.99 |
| 9 | 15.3% (9/59) | 5.1% (3/59) | 10.2% (−1.0% to 21.1%) | .125 |
| 10 | 22.0% (13/59) | 6.8% (4/59) | 15.2% (2.6%–27.8%) | .034 |
| 11 | 22.0% (13/59) | 5.1% (3/59) | 16.9% (4.7%–29.1%) | .013 |
| 12 | 20.7% (12/58) | 1.7% (1/59) | 19.0% (7.8%–30.2%) | .001 |

NOTE. Score >2 corresponding to symptoms causing at least mild discomfort measured by GSRS.

longest duration of symptoms was 1 hour and the median score of symptom severity was 2 (range, 1–4), corresponding with moderate symptoms on the day symptoms were most severe.

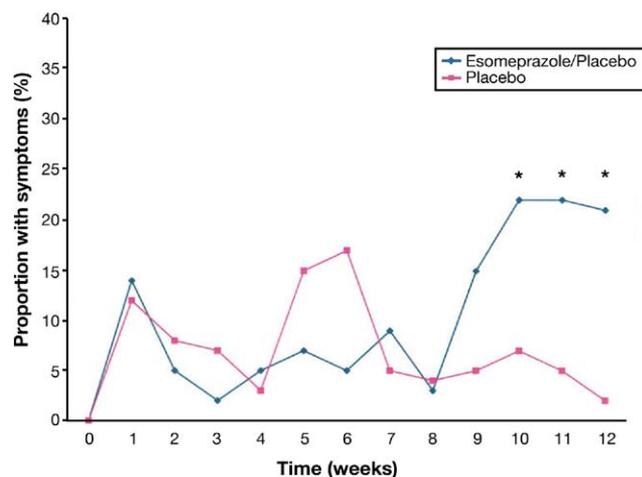Comparison of the SF-36 scores revealed no significant differences between the groups at 12 weeks.

Risk factors associated with development of symptoms after withdrawal of treatment were evaluated using multivariate logistic regression analysis. Gender, age, body mass index, smoking, excessive weekly alcohol consumption, *H pylori* status, or previous experience of acid regurgitation or dyspepsia were not significantly associated with an increased risk of acid-related symptoms after cessation of treatment. Any experience ever of heartburn before participating in the trial was associated with an odds ratio of 4.4 (95% CI, 1.4–13.6; $P = .01$) for development of acid-related symptoms in weeks 9–12.

P-gastrin was within normal range (<50 pmol/L) in both groups at weeks 0, 4, 8, and 12, but significantly higher in the PPI group during treatment with a difference of 14.0 pmol/l (95% CI, 9.8–18.2; $P < .001$) at week 4 and 17.3 pmol/l (95% CI, 12.7–22.0; $P < .001$) at week

8. P-gastrin in the PPI group increased significantly from week 0 to week 4 with a mean increase of 15.2 pmol/l (95% CI, 11.1–19.3; $P < .001$) with no further significant increase from week 4 to 8. The gastrin levels returned to baseline values by week 12 in the PPI group.

In the PPI group, P-gastrin was significantly correlated ($r_s = 0.34$; $P = .01$) with the combined GSRS score on heartburn, acid regurgitation, and dyspepsia at week 8 and was also correlated with GSRS reflux syndrome scale score ($r_s = 0.27$; $P = .04$) in week 10 (2 weeks after withdrawal of PPI). There was no significant correlation between P-gastrin and combined symptom score or reflux syndrome scale score in the placebo group.

P-CgA was within the normal range (<130 pmol/L) with no significant differences between the groups at baseline. At week 8, P-CgA was significantly higher and above the normal range in the PPI group with a mean of 147.3 ± 208.6 pmol/l compared with 53.4 ± 30.4 in the placebo group ($P < .001$). At week 12, the difference in P-CgA was still significant, with a mean of 106.8 ± 66.6 pmol/l in the PPI group compared with 74.5 ± 56.1 in the placebo group ($P = .02$). The mean CgA level in the PPI group was significantly higher at week 12 compared with baseline ($P < .001$).

## Discussion

The results of our study indicate and support the hypothesis that the RAHS is clinically significant. Treatment with a PPI (esomeprazole 40 mg once daily) for 8 weeks induces acid-related symptoms like heartburn, acid regurgitation, and dyspepsia once treatment is withdrawn. The symptoms observed in our trial caused mild to moderate discomfort and appeared for the majority of subjects in the first 2 weeks after withdrawal of PPI. The observation that >40% of healthy volunteers, who have never been bothered by heartburn, acid regurgitation, or dyspepsia, develop such symptoms in the weeks after cessation of PPI is remarkable and has potentially important clinical and economic implications. Even though symptoms are also observed in the placebo group, indicating increased attention to acid-related symptoms in the overall study population, the difference in the proportion with clinically relevant symptoms between the groups can only be explained by allocation to different interventions. This is supported by the timing of symp-



Score > 2 indicating at least mild discomfort measured by GSRS.
The PPI/placebo group received esomeprazole 40 mg o.d in weeks 1-8, followed by placebo in weeks 9-12.
The placebo group received placebo tablets in week 1-12.
* : P<.05

**Figure 1.** Temporal changes in the proportion of subjects with heartburn, acid regurgitation or dyspepsia.

toms occurring after blinded withdrawal of PPI in the final 4 weeks of the study in the actively treated group in contrast with the placebo group, where symptoms seemed to occur at random throughout the entire study period.

### Strengths and Weaknesses

The strengths of this study are the power and the double-blind, placebo-controlled design, including blinded withdrawal of PPI, making the subjects unaware of when to expect symptoms. Furthermore, the use of on-line reporting of symptoms with a thoroughly validated questionnaire within 24 hours has secured reliable and accurate monitoring of symptoms. One of the limitations of our study is the use of healthy volunteers as study subjects. We cannot be absolutely sure that symptoms develop as a consequence of RAHS to the same degree in patients, who have started PPI therapy because of dyspeptic symptoms. On the other hand, RAHS could be even more relevant in patients with reflux disease or other acid-related disorders. Within this population, it is likely that withdrawal of PPI treatment is difficult to achieve because of rapid recurrence of reflux symptoms that could be aggravated or maybe even provoked by RAHS.

### Comparison With Other Studies

Two studies have investigated occurrence of upper abdominal symptoms after withdrawal of treatment with a PPI, but both have only been published in abstract form so far. A small trial in 36 healthy volunteers investigated symptoms after treatment with a PPI for 14 days[23] and reported a significantly higher dyspepsia symptom score in a group treated with omeprazole in the 2nd week after withdrawal of treatment. The association between RAHS and the symptoms observed in that trial remains uncertain as a number of studies have failed to document acid rebound after withdrawal of only 2 weeks of PPI treatment.[24–26] In another trial with 48 subjects, a significantly higher proportion (44%) treated with pantoprazole 40 mg developed dyspepsia after withdrawal of 4 weeks of treatment compared with 9% in the placebo group.[27]

The symptoms observed in our trial have a more established physiologic foundation. Studies of acid output after 8 weeks to 3 months of treatment with different PPIs have shown an increase in basal acid output and maximal acid output 14 days after treatment compared with baseline values.[10,11,28] In a recent publication by Hunfeld et al,[29] studies on RAHS after therapy with PPIs were systematically reviewed. They concluded that there is some evidence for an increased capacity to secrete acid in H pylori-negative subjects after a minimum of 8 weeks of treatment.[29] Even though the studies in the review were all uncontrolled and used different measures for

acid secretory capacity, we still find it reasonable to claim that the symptoms observed in our trial are related to RAHS. This assumption is somewhat controversial, though. Other explanations than RAHS could be considered, especially because the correlation between gastric acid secretory capacity and acid-related symptoms is questionable. The fact that not all PPI-treated subjects experience acid-related symptoms after withdrawal could lead to the hypothesis that RAHS is only clinically relevant in subjects with a preexisting lower esophageal sphincter dysfunction and consequently the potential to reflux.

However, the fact that we observed a significant difference in both symptom scores and the proportion of subjects with symptoms from the 2nd week after discontinuation of PPI supports an association with RAHS either directly via acid secretion or indirectly via the changes in hormone levels associated with long-term PPI therapy.

Even moderate elevations in P-gastrin exert a trophic effect on the enterochromaffin-like cells and the increased P-CgA concentrations found in our study are likely to reflect functional or proliferative changes of the gastric enterochromaffin-like cells.[30,31] The continued occurrence of acid-related symptoms in the PPI group, even in the final week of the study at a time where P-gastrin levels had normalized, is possibly related to a sustained increased acid secretory capacity, as reflected by the increased levels of P-CgA.

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. Even though P-gastrin and P-CgA are only indirect measures of acid secretory capacity, we believe that these results support the hypothesis that RAHS is clinically relevant.

The proposed association is indirectly supported by previous studies showing that withdrawal of $H_2$-receptor antagonist therapy induces dyspectic symptoms in a proportion of previously asymptomatic subjects.[32]

It has been hypothesized that a lower gastric acid productive capacity associated with H pylori-induced gastric inflammation may protect infected subjects from development of acid rebound. Results of previous physiologic studies, which included a mixture of subjects with and without H pylori infection, have been contradictory.[10,28,33]

The randomly skewed allocation of the majority of infected subjects to the placebo group in our study does not allow us to determine if the acid rebound phenomenon is clinically significant in infected subjects. However, previous studies have shown that up to 75% of long-term treated patients in our region are not infected with H pylori,[34,35] which make our findings potentially relevant for the majority of these individuals.

### Clinical Implications

We recognize that the difference between the 2 groups in symptom scores is modest. However, considering the timing of symptoms and the double-blind, placebo-controlled design of this study, including blinded withdrawal of PPI, we believe that our findings is a very strong indication of a clinically significant acid rebound phenomenon that needs to be investigated in proper patient populations.

Although we cannot be certain that symptoms with the severity and frequency we observed in our study would make patients resume therapy, we know from clinical studies that even mild symptoms more than once a week constitutes troublesome symptoms.[36,37] The escape antacid medication used by the subjects treated with a PPI in our study attests to the clinical relevance of the observed symptoms. Pharmacoepidemiologic studies have shown that a significant proportion of patients treated long term with a PPI initiate and maintain therapy on uncertain or unapproved indications, such as functional dyspepsia, where the effects of acid-suppressive therapy is controversial.[2,6,38] Thus, patients with ambiguous symptoms that are not truly acid related may be prescribed a PPI empirically, but may find it difficult to withdraw from therapy because of the development of true acid-related symptoms related to acid rebound, necessitating continued PPI treatment.

The possible implications of RAHS need to be addressed in future studies. Tapering has been investigated in a clinical trial where long-term treated patients were randomised to tapering or instant discontinuation.[34] Tapering over 3 weeks did not have a significant effect on the proportion that successfully withdrew treatment compared with instant discontinuation. However, the duration of RAHS is unknown and probably lasts >3 weeks as suggested by the continued presence of acid-related symptoms 4 weeks after discontinuation of therapy (at week 12) in our study. Furthermore, 2 studies have shown increased acid secretory capacity ≥8 weeks after discontinuation of treatment.[10,39]

### Conclusion

Acid inhibition with a PPI for 8 weeks induces acid-related symptoms in a significant proportion of asymptomatic subjects when therapy is withdrawn. We find it highly likely that the symptoms observed in this trial are caused by RAHS and that this phenomenon is equally relevant in patients treated long term with PPIs. These results justify the speculation that PPI dependency could be 1 of the explanations for the rapidly and continuously increasing use of PPIs.

### Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2009.04.012.

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CLINICAL–ALIMENTARY TRACT

**Supplementary Figure 1.** Trial flow chart.