Proton Pump Inhibitor Therapy Improves Symptoms in Postnasal Drainage

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This article has an accompanying continuing medical education activity on page e11. Learning Objective: Upon completion of this exercise, successful learners will be able to appreciate the role of gastroesophageal reflux disease in patients presenting with extraesophageal symptoms.

BACKGROUND & AIMS: Gastroesophageal reflux is common among patients with postnasal drainage. We investigated whether proton pump inhibitor therapy improved symptoms in patients with postnasal drainage without sinusitis or allergies. **METHODS:** In a parallel-group, double-blind, multi-specialty trial, we randomly assigned 75 participants with continued symptoms of chronic postnasal drainage to groups that were given 30 mg of lansoprazole twice daily or placebo. Participants were followed up for 16 weeks. Symptoms were assessed at baseline and after 8 and 16 weeks. Ambulatory pH and impedance monitoring assessed presence of baseline reflux. The primary objective of the study was to determine if acid suppressive therapy improved postnasal drainage symptoms. The secondary objective was to assess if pH and impedance monitoring at baseline predicted response to treatment. **RESULTS:** Postnasal drainage symptoms improved significantly among patients given lansoprazole compared with placebo. After 8 and 16 weeks, participants given lansoprazole were 3.12-fold (1.28–7.59) and 3.50-fold (1.41–8.67) more likely to respond, respectively, than participants given placebo. After 16 weeks, median (interquartile) percent symptom improvements were 50.0% (10.0%–72.0%) for participants given lansoprazole and 5.0% (0.0%–40.0%) for participants given placebo ($P = .006$). Neither baseline presence of typical reflux symptoms nor esophageal physiologic parameters predicted response to therapy. **CONCLUSIONS: Among participants with chronic postnasal drainage without evidence of sinusitis and allergies, twice-daily therapy with proton pump inhibitors significantly improved symptoms after 8 and 16 weeks. The presence of heartburn, regurgitation, abnormal levels of esophageal acid, or nonacid reflux did not predict response to therapy.**

Keywords: Gastroesophageal Reflux Disease; Extraesophageal GERD; Randomized Controlled Trial; Impedance pH Monitoring.

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Postnasal drainage is a common symptom for which patients seek medical attention. It is defined as the sensation of drainage, pharyngeal irritation, and an urge to clear the throat.[1,2] Postnasal drainage is a normal physiologic process. However, when excessive, it is frequently attributed to sinonasal inflammatory disease and associated with chronic rhinosinusitis as well as allergic and nonallergic rhinitis. Postnasal drainage is the most common etiology for patients with persistent chronic cough and throat clearing.[3,4] The nonspecific and variable presentation of patients with rhinosinus diseases and lack of a diagnostic gold standard compound the difficult task of identifying the exact pathophysiologic source. Furthermore, given the chronic nature of the symptom and the added anxiety brought on by ineffective therapies, many continue seeking care and undergo costly medical or surgical treatment for sinonasal disease.

Gastroesophageal reflux disease is among the many potential purported causes of chronic postnasal drainage.[4,5] It is a common chronic disorder with increasing prevalence.[6] Approximately 40% of adults frequently report heartburn,[7] and it remains the leading outpatient physician diagnosis for gastrointestinal disorders in the United States.[8] Given its increasing prevalence, gastroesophageal reflux often coexists in many patients with chronic postnasal drainage. Esophageal acid exposure in this group may or may not be accompanied by presence of typical reflux symptoms such as heartburn and regurgitation.[9] Additional difficulty is the lack of a diagnostic gold standard for gastroesophageal reflux.[10] Upper gastrointestinal endoscopy, barium swallow, or ambulatory pH monitoring are commonly used but have a limited role in correctly diagnosing reflux as the cause in those with chronic postnasal drainage. Thus, the current clinical practice guidelines favor an empiric trial of a proton

Abbreviations used in this paper: QOLRAD, Quality of Life in Reflux and Dyspepsia; RAST, radioallergosorbent test; RSOM-31, Rhinosinusitis Outcome Measure; SNOT-20, Sino-Nasal Outcome Test.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.08.039

pump inhibitor over initial testing to treat presumptive gastroesophageal reflux.[11,12] Proton pump inhibitors are effective in suppressing the production of gastric acid, healing esophagitis,[13] and reducing symptoms of reflux. Previous controlled trials, however, have been disappointing regarding the beneficial effect of proton pump inhibitors in patients with chronic laryngitis, chronic asthma, and chronic cough.[14–18] Whether proton pump inhibitors improve the symptom of chronic postnasal drainage is less well established, and direct evidence is lacking.[11]

We compared lansoprazole with placebo in patients with poorly controlled chronic postnasal drainage without evidence of sinusitis or allergies. The primary objective of the study was to determine if acid suppressive therapy would improve postnasal drainage symptoms. The secondary objective was to assess if pH and impedance monitoring at baseline would predict response to treatment.

Patients and Methods

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The Vanderbilt Institutional Review Board approved this clinical trial (#051169) (NCT00335283). All participants signed an informed consent form before any study-related procedures were performed.

Participant Selection

We conducted a randomized, placebo-controlled, double-blind trial of lansoprazole (Prevacid; Takeda Pharmaceuticals North America, Inc, Chicago, IL) in participants with the symptom of chronic postnasal drainage. Inclusion criteria were age 18 years or older; a diagnosis of chronic rhinitis with the predominant symptom of postnasal drainage by an expert physician in a multidisciplinary allergy, asthma, and sinus clinic; a negative radioallergosorbent test (RAST) allergy panel (or skin test) or a positive RAST result (or skin test) but with an insufficient response to conventional therapies (allergen avoidance, topical nasal corticosteroids, allergy shots, antihistamines) (in clinical practice, this group is often subjected to gastroesophageal reflux disease therapy similar to those with a negative RAST test result); a negative computed tomographic scan of the sinuses (no opacification or air-fluid levels in frontal, maxillary, ethmoid, and sphenoid sinuses); and negative findings on anterior rhinoscopy (absence of pus, crusts on mucosal surfaces). Participants were excluded if they were younger than 18 years; were pregnant; had diagnoses of ciliary dyskinesia, cystic fibrosis, an immune deficiency, uncontrolled thyroid disease, acute sinusitis, or chronic rhinosinusitis; had undergone surgery for reflux or peptic ulcer disease; actively used a topical decongestant or took proton pump inhibitors within the past 30 days; or were taking drugs that could interact with proton pump inhibitors, such as theophylline, iron supplements, warfarin, antifungal drugs, or digitalis. Participants were also excluded if they could not tolerate proton pump inhibitors or had a serious illness that would interfere with study participation. Participants with isolated cough without postnasal drainage were not considered.

Study Design

The study was conducted as a single-center multidisciplinary trial involving the Vanderbilt Asthma, Sinus, Allergy Program and the Vanderbilt Digestive Disease Center from May 2006 to March 2009. The study was designed as a 2-group, parallel-design, double-blind, randomized trial to test the hypothesis that lansoprazole was superior to placebo in improving the symptom of postnasal drainage. Participants were randomly assigned (computer generated) in a 1:1 ratio to receive either lansoprazole 30 mg twice daily or a similar-appearing placebo for 16 weeks. Participants were instructed to take the medication 30 minutes before breakfast and 30 minutes before dinner. After randomization, participants returned to the clinic for assessment of outcome measures at 8 weeks and 16 weeks. Drug accountability, concomitant medication review, and statement of eventual adverse events were checked during the 8- and 16-week follow-up visits. Information regarding lifestyle modification for reflux was not administered and was not enforced. The investigators, patients, and those involved in obtaining outcome data were blinded to randomization status of the patients.

Screening Period

Participants who met eligibility criteria enrolled in a 2- to 4-week run-in period, during which they completed a baseline symptom questionnaire assessing demographics (age, sex, and race); presence, severity, and frequency of gastroesophageal reflux and reflux-associated symptoms (cough, hoarseness, throat clearing, sore throat, globus sensation, heartburn, regurgitation, problem swallowing, chest pain, and discomfort to talk); tobacco and alcohol use; and presence of voice/throat and nasal symptoms. Severity of gastroesophageal reflux and throat symptoms was scored using a 5-point Likert scale (0 = none; 4 = severe). Participants also underwent esophageal motility testing and ambulatory prolonged impedance pH monitoring while off acid suppressive therapies. The results from esophageal physiologic testing did not affect randomization.

Outcome Measures

The primary outcome measure was postnasal drainage symptom response measured by using a visual analogue scale. At 8 and 16 weeks, a horizontal symptoms scale from 0% (no change) to 100% (symptoms completely resolved) was presented to participants to assess improvement in postnasal drainage symptoms.

Secondary outcomes recorded at baseline and at 8 and 16 weeks were the Rhinosinusitis Outcome Measure (RSOM-31),[19] Sino-Nasal Outcome Test (SNOT-20),[20] and Quality of Life in Reflux and Dyspepsia (QOLRAD)[21] questionnaires. RSOM-31 is a 31-item rhinosinusitis-specific questionnaire that is clinically validated and reliable[19] and measures both symptom magnitude on a 5-point scale and symptom importance on a 4-point Likert scale. Scores range from 0 to 155 for magnitude and from 31 to 124 for importance, with the higher scores suggesting worse quality of life. SNOT-20 is a modification of the RSOM-31 questionnaire that is more focused on nasal and paranasal symptoms, including postnasal drainage.[20] It is a validated rhinosinusitis questionnaire containing 20 questions (ranging from 0 = no problems to 5 = problems as bad as can be). Scores are expressed between 0 to 100, with the higher score representing worse quality of life. QOLRAD is a validated gastroesophageal reflux disease–dedicated and self-administrated questionnaire.[21]

Esophageal Function Testing

High-resolution manometry (Sierra Scientific Instruments Inc, Los Angeles, CA) was used to measure the location of the lower esophageal sphincter before placement of the impedance pH catheter. Impedance pH monitoring (Sandhill Scientific Inc, Highlands Ranch, CO) was performed while participants were off proton pump inhibitor therapy for at least 7 days. The details for the conduct of both methods were previously described.[22]

Statistical Analysis

Data were collected and stored at the secure Web-based Vanderbilt Digestive Disease Center REDCap (Research Electronic Data Capture) (1 UL1 RR024975 NCRR/NIH). REDCap is an application designed to support data capture for research studies providing (1) an intuitive interface for validate data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources. There was strict control and supervision of the data entry and access for this study.

A sample size of 33 patients in each treated arm was considered sufficient to detect a difference of 35% between groups, assuming a lansoprazole treatment response of 70% and a placebo response of 35% with an α level of .05 and 90% power. A total of 75 patients was considered an adequate sample size to allow for a 10% dropout rate. All primary and secondary outcomes were measured on an ordinal scale, so we used the proportional odds logistic regression model to estimate the log odds of improved scores in the lansoprazole and placebo groups. For the RSOM-31, SNOT-20, and QOLRAD survey analyses, we adjusted for survey results collected at baseline to improve precision. Analyses of treatment effect modification by chief symptom (heartburn, regurgitation) and pH characteristics were performed by including interaction terms between the potential modifier and treatment in the model. All analyses were performed using completed data according to treatment assignment at randomization. Continuous variables are described using the median (interquartile range) and results presented as odds ratios (95% confidence interval) as estimated using the R statistics package.

Role of Funding Source

The protocol was an independent investigator-initiated study funded by Takeda Pharmaceuticals North America, Inc, but conceived by the primary investigator (M.F.V.) and coprimary investigators (D.C.L. and D.D.H.). Takeda Pharmaceuticals provided funding for the study coordinator and patient compensation and provided samples of lansoprazole and identical-appearing placebo. The funding source had no role in the study design, conduct, data collection, statistical analysis, manuscript preparation, interpretation, or decision to submit the manuscript for publication.

Results

A total of 75 participants were randomly assigned to one of the 2 groups in the study (Supplementary Figure 1). The majority of participants were white women. Nearly two thirds of participants had concomitant heartburn and one half of participants reported regurgitation at baseline. Baseline characteristics were similar between the placebo and lansoprazole groups (Table 1). The participants were nonsmokers, and more than half were using nasal corticosteroid or antihistamine medications, the dose or use of which was not altered during the study period. Only one third of participants had previously used proton pump inhibitor therapy. Ambulatory pH and impedance monitoring was performed in 65% of participants at baseline. Gastroesophageal reflux objectively assessed by pH monitoring was present in 30% of participants in the placebo group and 31% of participants in the lansoprazole group. Impedance parameters were abnormal in 9% of participants in the placebo group and 6% of the participants in the lansoprazole group. Fewer than half of the participants in each group had an abnormal esophageal motility pattern, but most were due to abnormalities in lower esophageal sphincter pressure (hypotensive or hypertensive). Eleven participants (5 in the placebo group and 6 in the lansoprazole group) were not included in the analysis due to adverse events (5 participants), noncompliance (2 participants), lost to follow-up (2 participants), and withdrawal of consent (2 participants). There was no evidence of any difference in the baseline demographic or physiologic parameters in the 11 participants not included in the analysis compared with those who completed the

Table 1. Baseline Characteristics of the Study Population

Characteristics	Placebo (n = 39)	Lansoprazole (n = 36)
Age at distribution (*y*)	48 (32–54)	33 (30–56)
Male sex (%)	35	20
Race or ethnic group (%)		
White	88	73
Black	9	16
Hispanic	0	3
Other	3	8
Current or former smoker (%)	3	0
Current use of nasal medication (%)		
Corticosteroid spray	65	77
Decongestants	32	20
Antihistamines	62	63
Previous acid suppressive therapy use (%)		
Proton pump inhibitor	32	37
H_2 receptor antagonist	30	20
Esophageal physiologic testing		
Participants assessed (%)	65	65
pH		
Abnormal[a] (%)	30	31
% total time pH <4	3.1 (1.2–6.8)	3.1 (1.6–5.9)
% upright time pH <4	3.9 (1.0–7.0)	4.7 (1.9–9.7)
% supine time pH <4	0.2 (0.0–2.6)	0.3 (0.0–2.7)
Impedance		
Abnormal[b] (%)	9	6
Total no. of reflux events	45 (30–61)	46 (44–57)
Acid reflux events	35 (16–42)	32 (23–43)
Non–acid reflux events	11 (6–18)	8 (5–19)
Motility (%)		
Abnormal	48	40
Hypotensive LES	24	7
Ineffective motility disorder	10	0
Hypertensive LES	14	33
RSOM-31		
Total score[c]	51 (38–69)	63 (50–93)
Nasal	11 (9–15)	15 (13–20)
Eye	4 (0–6)	4 (1–6)
Sleep	11 (7–13)	10 (6–15)
Ear	4 (2–9)	5 (2–11)
General	11 (6–17)	14 (11–20)
Practical	8 (4–11)	9 (4–12)
Emotional	3 (2–5)	5 (2–8)
SNOT-20		
Total score[d]	35 (31–45)	36 (31–52)
Nasal	10 (8–12)	12 (8–14)
Postnasal discharge	2 (1–3)	3 (2–3)
QOLRAD		
Total score[e]	160 (142–170)	155 (126–169)
Emotional	41 (35–42)	37 (26–41)
Sleep	33 (27–35)	31 (23–35)
Food/drink	36 (30–41)	34 (24–39)
Physical/social	34 (31–35)	33 (30–35)
Vitality	19 (16–21)	18 (13–21)
Other self-reported conditions (%)		
Cough	62	73
Hoarseness	47	50
Throat clearing	85	93
Sore throat	58	65
Globus	63	70
Heartburn	65	67
Regurgitation	44	53
Problem swallowing	44	40
Chest pain	24	30
Discomfort to talk	32	40

NOTE. Results are expressed as median (interquartile range) unless otherwise noted.
LES, lower esophageal sphincter.
[a]Abnormal pH defined as percent time pH < 4 of greater than 5.5%.
[b]Abnormal impedance defined by total number of reflux events greater than 72.
[c]Score range from 0 to 155 for magnitude and from 31 to 124 for importance, with the higher scores suggesting worse quality of life.
[d]Score range from 0 to 100, with the higher scores suggesting worse quality of life.
[e]Score range from 25 to 175, with the higher scores suggesting less impaired quality of life.

study. No additional medications for allergies or for reflux disease were allowed or used during the study period.

When defining an adherent participant as one who took both doses of the drug or placebo on at least 80% of the days during the study period, the rate of participants who reported adherence in the lansoprazole group was similar to the rate in the placebo group (90% and 91%, respectively) and as assessed by pill counts (85% and 87%, respectively). Lansoprazole was generally well tolerated, and only a few participants discontinued treatment in either the lansoprazole or placebo group due to side effects (3 vs 2 participants). The most commonly reported adverse events in patients randomized to lansoprazole or placebo included abdominal pain, nausea, and bloating in the former and heartburn and cough in the latter groups. There were no serious adverse events requiring urgent or emergent care or hospitalization in either group.

Outcome

Overall, the participants had significant improvement in the primary symptom of postnasal drainage with lansoprazole compared with placebo both at 8 and 16 weeks (Table 2). At 8 and 16 weeks, participants treated with lansoprazole were 3.12 (1.28–7.59) and 3.50 (1.41–8.67) times more likely to respond than participants receiving placebo, respectively. Median symptom score improvement at 8 and 16 weeks was 55.0 (12.5–80.0) and 50.0 (10.0–72.0), respectively, for participants treated with lansoprazole and 3.5 (0.0–53.8) and 5.0 (0.0–40.0), respectively, for participants receiving placebo. SNOT-20 scores were 2.44 (0.95–6.31) and 4.51 (1.50–13.6) times more likely to improve at 8 and 16 weeks, respectively, for participants treated with lansoprazole than those receiving placebo (Table 2). QOLRAD scores were 5.17 (2.02–13.2) and 5.31 (1.97–14.3) times more likely to improve at

Table 2. Primary and Secondary Outcomes

Outcomes	Placebo (n = 34)	Lansoprazole (n = 30)	Treatment effect[a]	*P* value
8 weeks				
Postnasal drainage				
Symptom improvement[b]	3.5 (0.0–53.8)	55.0 (12.5–80.0)	3.12 (1.28–7.59)	.01
>50% improvement (%)[c]	35	53	1.73 (0.65–4.60)	.27
RSOM-31[d]	36 (20–60)	40 (23–65)	1.01 (0.38–2.70)	.97
SNOT-20[d]	32 (17–39)	25 (17–35)	2.44 (0.95–6.31)	.06
QOLRAD[d]	155 (148–170)	174 (157–175)	5.17 (2.02–13.2)	.006
16 weeks				
Postnasal drainage				
Symptom improvement[b]	5.0 (0.0–40.0)	50.0 (10.0–72.0)	3.50 (1.41–8.67)	.006
>50% improvement (%)[c]	24	60	4.87 (1.66–14.30)	.003
RSOM-31[d]	35 (23–55)	35 (21–61)	1.11 (0.40–3.06)	.84
SNOT-20[d]	27 (16–38)	20 (19–40)	4.51 (1.50–13.6)	.007
QOLRAD[d]	160 (146–172)	173 (158–174)	5.31 (1.97–14.3)	.001

[a]Odds ratio and 95% confidence interval.
[b]Median (interquartile range).
[c]Percentage of subjects who experienced at least 50% symptom improvement.
[d]Median (interquartile range) and odds ratios of total score improvement adjusted for baseline scores.

8 and 16 weeks for participants treated with lansoprazole than those receiving placebo. RSOM-31 scores were not significantly affected in participants treated with lansoprazole compared with those receiving placebo.

Subgroup Analyses

We performed planned subgroup analyses to determine if a subgroup of participants was more likely to benefit from lansoprazole therapy. Neither baseline presence of typical reflux symptoms such as heartburn and regurgitation nor esophageal physiologic parameters of motility, pH, or impedance monitoring predicted increased likelihood of response to therapy.

Discussion

The purpose of this trial was to determine if acid suppression using a proton pump inhibitor, lansoprazole, would improve the symptom of chronic postnasal drainage. We showed that in participants without objective signs of chronic sinusitis or allergies with chronic postnasal drainage as the main symptom, a trial of acid suppression would be beneficial. We used twice-daily lansoprazole to ensure adequate acid suppression[23] and the study duration was chosen based on prior reports that symptomatic improvement in extraesophageal reflux may take up to 16 weeks.[9,11,24] In this study, we found that clinical benefit, although stronger at 16 weeks, was apparent even after 2 months of therapy. Moreover, we performed ambulatory pH and impedance monitoring studies to establish whether those with documented acid or nonacid reflux might benefit more from therapy with a proton pump inhibitor than those without objective pH or impedance findings. We did not identify any predictors of treatment response, which is concordant with the fact that the tests are not the gold standard for diagnosis of gastroesophageal reflux.

Proton pump inhibitors have previously shown clinical benefit in healing esophagitis and improving symptoms in patients with nonerosive reflux disease.[13] However, their benefit has been difficult to establish in patients with suspected extraesophageal reflux symptoms in randomized controlled trials.[14–18] A recent double-blind placebo-controlled study by the American Lung Association Asthma Clinical Research Centers[16] in 412 participants with inadequately controlled asthma and minimal or no symptom of gastroesophageal reflux found no benefit of treatment with high-dose esomeprazole. Similarly, Kiljander et al[17] found no overall benefit in daily expiratory flow rate or exacerbations of asthma symptoms using high-dose esomeprazole for 24 weeks in patients with asthma. The study on chronic laryngitis suspected of being reflux related with the largest number of enrolled participants found no evidence that esomeprazole 40 mg administered twice daily for 16 weeks was more effective than placebo in resolving or improving laryngeal signs and symptoms.[14] A meta-analysis of 8 pooled randomized controlled trials in chronic laryngitis showed similar findings.[15] Despite the results of these trials, it is largely accepted that gastroesophageal reflux may exacerbate many extraesophageal symptoms.[9,25,26] The overwhelming challenge in most studies has been to enroll the patient population most likely to benefit from acid suppressive therapy. However, this has proven difficult due to the lack of a gold standard for reflux disease. pH monitoring, once considered the gold standard, has poor sensitivity and laryngoscopy has poor specificity.[9,10,27]

This study differs from previous trials[5,14–18] in that we first excluded patients with objective evidence for other potential causes for chronic postnasal drainage. Patients with chronic sinusitis and those with significant allergies were excluded. Additionally, baseline presence or absence of concomitant heartburn did not play a role in patient

enrollment, unlike two of the trials.[14,16] The role of "silent reflux" in patients with predominately extraesophageal symptoms is currently controversial.[11] We found that neither baseline presence of typical reflux symptoms such as heartburn and regurgitation nor esophageal physiologic parameters of motility, pH, or impedance monitoring predicted increased likelihood of response to therapy. In addition to patient report of postnasal drainage symptom improvement, we used a validated questionnaire for reflux and rhinosinus diseases. Postnasal drainage symptom improvement was chosen as the primary outcome because it is similar to current clinical practice in assessing response to therapy. Validated questionnaires were needed, however, to provide support for the measured outcome. The improvement in the symptom of postnasal drainage on proton pump inhibitor therapy in this study was paralleled by improvement in SNOT-20 as well as QOLRAD but not RSOM-31. SNOT-20 was derived from RSOM-31 to be a more specific instrument for rhinosinus disease, allowing the patients to indicate which items are most important to them, independent of the magnitude of the problem.

Proposed means by which gastroesophageal reflux may induce extraesophageal symptoms have traditionally included microaspiration of gastric or duodenal contents and stimulation of a vagal reflex arc.[28] Thus, one mechanism by which proton pump inhibitors may result in improvement of chronic postnasal drainage may be reduction in gastric acidity and volume. Previous studies have shown normalization of esophageal acid exposure in 99% of patients treated with proton pump inhibitors twice daily.[11,22] Moreover, proton pump inhibitor therapy has been shown to reduce not only esophageal acid exposure but also esophageal nonacid reflux,[29,30] most likely due to gastric volume reduction.[31,32] However, alternative mechanisms for the observed improvement in postnasal drainage symptoms deserving special attention are the potential antihistaminergic effect of drying nasopharyngeal secretions and/or the anti-inflammatory effect of proton pump inhibitors.[33] Several in vitro as well as in vivo studies have suggested that proton pump inhibitors exert anti-inflammatory effects exclusive of gastric acid inhibition.[34–38] Omeprazole and lansoprazole were found to have antioxidant effects by preventing the oxidation of β-carotene by hypochlorous acid and the copper-induced oxidation of low-density lipoproteins, respectively.[34,35] Proton pumps present in the phagolysosomes of neutrophils inhibited by these agents may result in inhibition of oxidative burst and subsequent attenuation or prevention of inflammation.[36,37] In vitro studies have also shown that omeprazole impaired neutrophil migration and phagocytosis.[36] Proton pump inhibitors also exert anti-inflammatory effects by inhibiting the production of proinflammatory cytokines such as interleukin-8,[37] interleukin-6, and tumor necrosis factor α.[38]

Our study has several limitations. First, the sample size of 75 participants is relatively small. However, the study was designed to exclude those with other potential causes for symptoms of postnasal drainage, which resulted in increased selectivity of participants. A total of 372 subjects with postnasal drainage as the primary symptom were evaluated, from which 75 participants were randomized (Supplementary Figure 1). Second, lack of an objective measure of postnasal drainage limited the study outcome to be symptom based only. However, inclusion of validated quality-of-life questionnaires increased the robustness of the results and the study conclusions. Third, baseline pH and impedance monitoring were performed in 65% of patients, which may have decreased our precision to determine if initial pH modified the effect of lansoprazole on postnasal drainage symptoms. However, given the discomfort associated with these tests, we could not mandate testing for all potential candidates risking decreased enrollment.

In conclusion, we have found that among patients with chronic postnasal drainage without evidence of sinusitis and allergies, twice-daily proton pump inhibitor therapy resulted in significant improvement at 8 and 16 weeks. There was no evidence that presence of typical symptoms, heartburn or regurgitation, or abnormal esophageal acid, acid or nonacid exposure, modified response to therapy.

Supplementary Material

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.2010.08.039.

References

1. Morice AH. Post nasal drip syndrome—a symptom to be sniffed at? Pulm Pharmacol Ther 2004;17:343–345.
2. O'Hara J, Jones NS. Post nasal drip syndrome: most patients with purulent nasal secretions do not complain of chronic cough. Rhinology 2006;44:270–273.
3. Palombini BC, Villanova CAC, Araujo E, et al. A pathogenic triad in chronic cough-asthma, postnasal drip syndrome and gastroesophageal reflux disease. Chest 1999;116:279–284.
4. Wise, SK, Wise JC, DelGaudio JM. Association of nasopharyngeal and laryngopharyngeal reflux with postnasal drip symptomatology in patients with and without rhinosinusitis. Am J Rhinol 2006;20: 283–289.
5. Pawar S, Lim HJ, Gill M, et al. Treatment of postnasal drip with proton pump inhibitors. Am J Rhinol 2007;21:695–701.
6. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54: 710–717.
7. Locke GR, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448–1456.
8. Shaheen N, Hansen R, Morgan D, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101: 2128–2138.

9. Frye JW, Vaezi MF. Extraesophageal GERD. Gastroenterol Clin North Am 2008;37:845–858.
10. Vaezi MF. The role of pH monitoring in extraoesophageal gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006;231: 40–49.
11. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008;135: 1383–1413.
12. Kenneth R. DeVault DOC. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005;100:190–200.
13. Doonellan C, Sharma N, Preston C, et al. Medical treatment for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev 2005;2: CD003245.
14. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole: placebo controlled trial. Laryngoscope 2006;116:254–260.
15. Qadeer MA, Phillips CO, Lopez AR, et al. Proton pump inhibitor therapy for suspected GERD-related laryngitis: a meta analysis of randomized controlled trials. Am J Gastroenterol 2006;101: 2646–2654.
16. The American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med 2009;360:1487–1499.
17. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40mg twice daily on asthma: a randomized placebo controlled tiral. Am J Respir Crit Care Med 2006;173:1091–1097.
18. Chang AB, Lasserson TJ, Kiljander TO, et al. Systematic review and meta-analysis of randomized controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. BMJ 2006;332:11–17.
19. Piccirillo JF, Edwards D, Haiduk A, et al. Psychometric and clinimetric validity of the 31-item rhinosinusitis outcome measure (RSOM-31). Am J Rhinol 1995;9:297–306.
20. Piccirillo JF, Merritt MG, Richards ML. Psychometric and clinimetric validity of the 20-item sino-nasal outcome test (SNOT-20). Otolaryngol Head Neck Surg 2002;126:41–47.
21. Wiklund IK, Junghard O, Grace E, et al. Quality of life in reflux and dyspepsia patients. Psychometric documentation of a new disease specific questionnaire (QOLRAD). Eur J Surg 1998; 164:41–49.
22. Pritchett JM, Aslam M, Slaughter JD, et al. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. Clin Gastroenterol Hepatol 2009;7:743–748.
23. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol 2005;100:283–289.
24. Belafsky PC, Postma GN, Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical findings. Laryngoscope 2001;111:979–981.
25. El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997;113:755–760.
26. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut 2007;56:1654–1664.
27. Vaezi MF, Hicks DM, Abelson TI, et al. Laryngeal signs and symptoms and gastroesophageal reflux disease: a critical assessment of cause and effect association. Clin Gastroenterol Hepatol 2003;1:333–344.
28. Shaker R. Protective mechanisms against supraesophageal GERD. Clin Gastroenterol 2000;30:S3–S8.
29. Champion G, Richter JE, Vaezi MF, et al. Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology 1994;107:747–754.
30. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001;120:1599–1606.
31. Babaei A, Bhargava V, Aalam S, et al. Effect of proton pump inhibition on the gastric volume: assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2009;29:863–870.
32. Gursoy O, Memiş D, Sut N. Effect of proton pump inhibitors on gastric juice volume, gastric pH and gastric intramucosal pH in critically ill patients: a randomized, double-blind, placebo-controlled study. Clin Drug Investig 2008;28:777–782.
33. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implication. Dig Dis Sci 2009;54:2312–2317.
34. Lapenna D, de Gioia S, Ciofani G, et al. Antioxidant properties of omeprazole. FEBS Lett 1996;382:189–192.
35. Blandizzi C, Fornai M, Colucci R, et al. Lansoprazole prevents experimental gastric injury induced by non-steroidal anti-inflammatory drugs through a reduction of mucosal oxidative damage. World J Gastroenterol 2005;11:4052–4060.
36. Wandall JH. Effects of omeprazole on neutrophil chemotaxis, super oxide production, degranulation and translocation of cytochrome b-245. Gut 1992;33:617–621.
37. Handa O, Yoshida N, Fujita N, et al. Molecular mechanisms involved in anti-inflammatory effects of proton pump inhibitors. Inflamm Res 2006;55:476–480.
38. Sasaki T, Yamaya M, Yasuda H, et al. The proton pump inhibitor lansoprazole inhibits rhiovirus infection in cultured human tracheal epithelial cells. Eur J Pharmacol 2005;509:201–210.

Received May 25, 2010. Accepted August 19, 2010.

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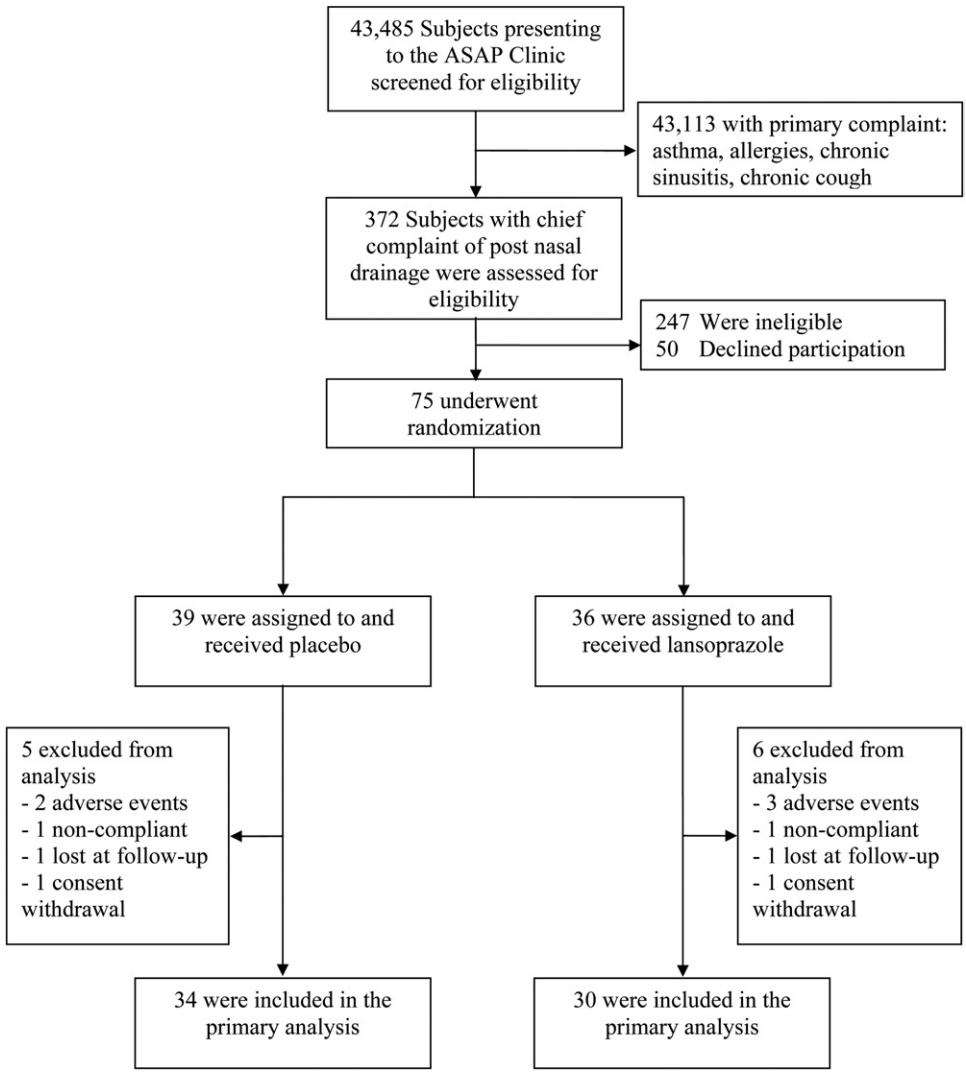
Conflicts of interest

The authors disclose the following: Dr Vaezi received research grant support from Takeda Pharmaceuticals North America, Inc, for the conduct of this study. The remaining authors disclose no conflicts.



Supplementary Figure 1. Enrollment, randomization, and follow-up of study participants.