

Lansoprazole Compared With Ranitidine for the Treatment of Nonerosive Gastroesophageal Reflux Disease

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Background: Traditionally, proton pump inhibitors are used primarily for patients with esophagitis. However, patients with nonerosive reflux disease may also benefit from these powerful medications.

Objective: To compare the safety and symptom relief efficacy of lansoprazole with ranitidine therapy and with placebo.

Methods: In 2 randomized, double-blind, multicenter trials of 901 patients with symptomatic reflux disease, which was confirmed by endoscopy to be nonerosive, received lansoprazole, 15 or 30 mg once daily; ranitidine, 150 mg twice daily; or placebo for 8 weeks.

Results: Analysis of daily diary data during the first 4 weeks and for the entire 8 weeks of treatment revealed that patients who were treated with either dosage of lansoprazole reported significantly ($P < .05$) lower

percentages of days and nights with heartburn, less pain severity of both day and night heartburn, fewer days of antacid use, and smaller amounts of antacid use compared with patients who were treated with ranitidine or placebo. The incidence of possible or probable treatment-related adverse reactions was comparable among the treatment groups; abdominal pain and diarrhea were the most commonly reported adverse events. No statistically significant differences were noted between treatment groups in laboratory analyses.

Conclusion: Lansoprazole therapy is more effective than standard dosages of ranitidine or placebo in relieving symptoms in patients with endoscopically confirmed nonerosive reflux esophagitis.

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GASTROESOPHAGEAL reflux disease (GERD) is a ubiquitous, chronic disorder that may cause a significant decrease in patient functioning and quality of life and an increase in the risk for esophageal damage. While a large percentage of individuals report occasional or monthly heartburn,¹ approximately 20% of the US adult population experiences reflux symptoms on a weekly basis.² A recent study found that the presence of weekly heartburn symptoms has a significant negative impact on patients' physical and mental functioning.¹

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Gastroesophageal reflux is rarely an acute or transient event, but rather a chronic disease with symptoms that either remain stable or slowly increase in severity and/or frequency. A recent study found that individuals with reflux continued to experience symptoms when re-polled 7 years later.³ These symptoms can

have a more profound impact on patient quality of life than duodenal ulcers, untreated hypertension, mild congestive heart failure, angina, or menopause.⁴

Chronic reflux of the acidic gastric contents into the esophagus produces a wide spectrum of clinical symptoms and manifestations. These can range from mild episodic symptoms of heartburn and regurgitation without macroscopic esophagitis to chronic inflammation and ulceration; severe cases may involve stricture or hemorrhage.^{5,6} Unfortunately, from a diagnostician's viewpoint, with regard to symptom severity, patients with less severe grades of esophagitis do not differ from those with more severe forms.⁷ Therefore, prompt and effective reduction of esophageal mucosal exposure to the acidic gastric contents is the basis for reducing patient symptoms; if erosions are present, the esophagitis needs to be healed.

Antisecretory agents, such as proton pump inhibitors and histamine-2 receptor antagonists (H2RAs), have been found to decrease the symptoms of heartburn and, when present, heal esophagitis.⁸⁻¹⁴ Proton pump inhibitor therapy produces symp-

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STUDY DESIGN, PATIENTS, AND METHODS

STUDY DESIGN

Two phase III, multicenter (37 investigative sites in each trial), randomized, active-controlled, double-blind, parallel-group studies compared the safety and efficacy of 8 weeks of lansoprazole therapy, 15 mg once daily, and lansoprazole therapy, 30 mg once daily, with the efficacy of ranitidine therapy, 150 mg twice daily, in patients with endoscopically confirmed, symptomatic, nonerosive (grade 0 or 1 esophagitis) reflux disease. The study procedures and designs were identical except for the inclusion of a placebo group in one of the two studies. Antacid tablets (Gelusil [9.7 mmol of acid neutralizing capacity per tablet]; Parke-Davis, Morris Plains, NJ) were also supplied to each patient to be taken on an as-needed basis for the relief of reflux symptoms.

PATIENT SELECTION

Study randomization occurred after a 7- to 10-day pretreatment period, during which patients recorded the frequency and severity of day and night heartburn. Patients who recorded moderate to severe day and/or night heartburn for at least 50% of the days during the pretreatment period and reported moderate to severe day and/or night heartburn for more than 50% of the days over the past 6 months prior to study entry were considered eligible for study inclusion. At the baseline visit, patients were required to have endoscopically proven nonerosive reflux disease of grade 0 or 1 esophagitis (grade 0 was defined as normal mucosa and grade 1 was defined as mucosal edema, hyperemia, and/or friability of mucosa).

Patients were excluded from study participation if they had any of the following: Barrett esophagus; duodenal and/or gastric ulcer 3 mm in diameter or larger; esophageal stricture requiring dilation; coexisting systemic disease affecting the esophagus (eg, scleroderma); history of gastrointestinal bleeding or gastric, duodenal, or esophageal surgery; clinically significant diseases involving major organs; clinically significant abnormal laboratory values; evidence of current alcohol abuse or illegal drug use; long-term use of ulcerogenic drugs, including nonsteroidal anti-

inflammatory drugs, corticosteroid therapy (the equivalent of >10 mg of prednisone per day), or aspirin (>325 mg per day); use of an H2RA, anticholinergic, and/or prokinetic agent during the pretreatment period; use of a proton pump inhibitor during the pretreatment period; or use of any investigational drug within 12 weeks prior to initiating study treatment. Female subjects of childbearing potential agreed to continued use of an appropriate means of contraception, were nonlactating, and had a negative serum pregnancy test result. Eligible subjects were not to have received any blood products within 12 weeks of initiating the study. Approval for the study was obtained from the human studies committee at each participating investigative site. Written informed consent was obtained prior to each patient's enrollment into the study.

TREATMENT RANDOMIZATION

Patients meeting the inclusion criteria in the comparative trial including placebo were randomized in a 2:2:2:1 ratio to 1 of the 4 treatment groups (lansoprazole, 15 mg once daily; lansoprazole, 30 mg once daily; ranitidine, 150 mg twice daily; or placebo). Patients enrolled in the second comparative study were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups (lansoprazole, 15 mg once daily; lansoprazole, 30 mg once daily; or ranitidine, 150 mg twice daily). Lansoprazole, ranitidine, and placebo were supplied to patients as identical gray, opaque capsules. Patients were instructed to self-administer one capsule prior to breakfast and dinner.

PRETREATMENT AND STUDY EVALUATIONS

Pretreatment Evaluations

During the pretreatment period (7-10 days prior to study day 1), patients completed daily diaries to determine eligibility, reported a complete medical history, and underwent a complete physical examination, including vital sign assessment and laboratory analyses.

Study Evaluations

Endoscopy was performed in all patients at study day 1 prior to dosing to document the absence of erosive (grade 2 or

tom relief and healing earlier and more effectively than either standard or high-dose H2RA therapy.¹⁰ The superior efficacy of proton pump inhibitor therapy compared with H2RA therapy may be the result of the differences in the mechanism of action (H2RAs do not block meal-stimulated acid secretion) as well as the potential for the development of tolerance of H2RAs.^{11,15,16}

Clinical studies have demonstrated that proton pump inhibitors are more effective than H2RAs in the treatment of severe reflux disease.¹⁰ However, most patients with GERD have milder nonerosive forms of the disease. Our studies were designed to measure the safety and effectiveness of a proton pump inhibitor (lansoprazole; Takeda Abbott Pharmaceuticals, Deerfield, Ill) vs an H2RA (ranitidine; Glaxo Wellcome, Research Triangle Park, NC) or placebo in milder (nonerosive) forms of GERD.

RESULTS

STUDY POPULATION

A total of 925 patients were enrolled in the 2 studies: lansoprazole, 15 mg once daily (n=284); lansoprazole, 30 mg once daily (n=288); ranitidine, 150 mg twice daily (n=283); and placebo (n=70). Patients with esophagitis (grade >1) or Barrett esophagus at baseline were excluded from the intent-to-treat analysis. In addition, patients were not included in the intent-to-treat analysis if no diary data were recorded during the treatment period. Eight hundred ninety-eight patients were included in the intent-to-treat patient efficacy analysis. Among these patients, the 3 active treatment groups (ie, lansoprazole, 15 mg; lansoprazole, 30 mg; and raniti-

higher) esophagitis. Three gastric biopsy specimens were obtained at the time of endoscopy to assess *Helicobacter pylori* status. Endoscopy also documented the presence or absence of duodenal and/or gastric ulcer(s). At the study day 1 visit, qualifying patients were randomized to a treatment group, dispensed study medication and Gelusil, and given a treatment diary.

In the daily treatment diary, patients were instructed to document day and night heartburn (graded as none, mild, moderate, or severe), as well as frequency of Gelusil use and self-administration of study medication.

Patients returned after 4 and 8 weeks of treatment. Daily diaries were also collected and reviewed at these visits.

SAFETY AND COMPLIANCE EVALUATIONS

Safety

Safety of the treatment was monitored by complete physical examination, adverse event assessments, vital sign determinations (including blood pressure after 3 minutes in the sitting position, pulse rate after at least 30 seconds, respiratory rate, temperature, and body weight), and routine laboratory evaluations (including hematologic testing, serum chemistry testing, urinalysis, pregnancy testing in women, and theophylline and digoxin level determinations in patients taking these medications). Patients were required to have fasted for at least 8 hours prior to blood sampling for laboratory analyses. The clinical laboratory tests were analyzed at a central laboratory (Covance Central Laboratory Services, Indianapolis, Ind).

Investigators recorded their opinion of every adverse event reported as having a probable or possible relationship or no relationship to the study drug. Assigning a probable relationship to a study drug meant that, in the investigator's opinion, the adverse event had a timely relationship to study drug administration and no alternative cause of the adverse event was apparent. A possible relationship to a study drug meant that, in the investigator's opinion, a potential alternative cause of the adverse event existed.

Compliance

All patients were requested to bring their remaining drug supplies to the week-4 and week-8 visits. All remaining

capsules were counted to assess compliance with the prescribed regimen.

STATISTICAL ANALYSIS

Baseline demographic data, clinical characteristics, and gastrointestinal history were compared among the treatment groups using χ^2 tests for categorical variables and a one-way analysis of variance for continuous variables. Height and body weight were analyzed separately for men and women.

The primary efficacy variables were the assessments of daytime and nighttime heartburn and antacid usage as recorded in the patient diaries. The Wilcoxon 2-sample test was used for treatment group comparisons of the mean severity of day and night heartburn, the percentage of days and nights with heartburn, and the percentage of days and amount of antacid usage. In addition, treatment group comparisons of the average daily severity and percentage of days with day heartburn and night heartburn during the entire 8-week treatment period were performed, controlling for baseline heartburn severity, *H pylori* status during the pretreatment period, investigator, and demographic characteristics using the van Elteren method of combining Wilcoxon test results from independent strata.¹⁷ Heartburn severity of none, mild, moderate, and severe was scored as 0, 1, 2, and 3, respectively. Additionally, a multiple linear regression analysis of daytime and nighttime heartburn was performed to identify factors that might significantly influence symptom relief. The factors included in the model were treatment, baseline heartburn severity, *H pylori* status at baseline, age, sex, race, and lifestyle considerations (alcohol use, caffeine use, and tobacco use). Results from the intent-to-treat analyses for efficacy are presented.

The proportions of patients reporting adverse events were compared between treatment groups using the Fisher exact test. Treatment group comparisons of the mean change of laboratory values and vital signs from baseline to the final treatment visit were based on contrasts within the one-way analysis of variance with treatment groups as the factor. Treatment group comparisons for efficacy and safety were made between each dosage of lansoprazole and ranitidine or placebo.

dine, 150 mg) were comparable at baseline with respect to age; sex; race; tobacco, alcohol, and caffeine use; and *H pylori* status (**Table 1**). Male and female patients in each treatment group were also comparable with regard to height and weight.

Patients randomized to receive treatment with either dosage of lansoprazole, ranitidine, or placebo were comparable at baseline for frequency and severity of day or night heartburn and frequency of antacid use (**Table 2**). Patients randomized to receive placebo and lansoprazole, 30 mg, reported a higher mean number of antacid tablets taken per day compared with those randomized to receive lansoprazole, 15 mg. Patients randomized to receive lansoprazole, 30 mg, reported a significantly lower average daytime heartburn severity at baseline compared with those randomized to receive placebo ($P = .04$).

A total of 98 enrolled patients prematurely withdrew from the study. The occurrence of premature discontinuations among active treatment groups was similar: 29 (10%) of 284 patients receiving lansoprazole, 15 mg once daily; 26 (9%) of 288 patients receiving lansoprazole, 30 mg once daily; 28 (10%) of 283 patients receiving ranitidine, 150 mg twice daily; and 15 (21%) of 70 patients receiving placebo. The most common reasons for premature discontinuation included adverse events (8 patients from the lansoprazole, 15 mg once daily, group; 8 from the lansoprazole, 30 mg once daily, group; 10 from the ranitidine, 150 mg twice daily, group; and 6 from the placebo group) and therapeutic failure (5 patients from the lansoprazole, 15 mg once daily, group; 2 from the lansoprazole, 30 mg once daily, group; 5 from the ranitidine, 150 mg twice daily, group; and 6 from the placebo group).

Table 1. Baseline Characteristics of the Intent-to-Treat Population

Characteristic	No. of Patients (%)				P*
	Placebo (n = 67)	Ranitidine, 150 mg Twice Daily (n = 278)	Lansoprazole, 15 mg Once Daily (n = 276)	Lansoprazole, 30 mg Once Daily (n = 277)	
Age, mean ± SD, y (range)	46.3 ± 13.9 (23-84)	45.2 ± 13.2 (21-82)	44.9 ± 13.6 (20-81)	45.1 ± 12.7 (18-86)	.90*
Sex					.61†
Male	30 (44.8)	108 (38.8)	115 (41.7)	122 (44.0)	
Female	37 (55.2)	170 (61.2)	161 (58.3)	155 (56.0)	
Race					.21†
White	60 (89.6)	223 (80.2)	219 (79.3)	213 (76.9)	
Black	2 (3.0)	35 (12.6)	32 (11.6)	33 (11.9)	
Hispanic	0 (0)	17 (6.1)	19 (6.9)	24 (8.7)	
Other	5 (7.5)	3 (1.1)	6 (2.2)	7 (2.5)	
Tobacco					.33†
User	19 (28.4)	69 (24.8)	75 (27.2)	88 (31.8)	
Nonuser‡	48 (71.6)	209 (75.2)	201 (72.8)	189 (68.2)	
Caffeine					.37†
User	58 (86.6)	232 (83.4)	222 (80.4)	237 (85.6)	
Nonuser	9 (13.4)	46 (16.5)	54 (19.6)	40 (14.4)	
Alcohol					.77†
User	35 (52.2)	126 (45.3)	132 (47.8)	129 (46.6)	
Nonuser§	32 (47.8)	152 (54.7)	144 (52.2)	148 (53.4)	
<i>Helicobacter pylori</i> status					.32†
Positive	9 (13.4)	63 (22.7)	66 (23.9)	66 (23.8)	
Negative	56 (83.6)	212 (76.2)	206 (74.6)	209 (75.4)	

*From F test.

†From χ^2 test.

‡Includes ex-tobacco users.

§Includes ex-alcohol drinkers.

Table 2. Summary of Median Diary Data at Baseline

Variable	Placebo (n = 67)	Ranitidine, 150 mg Twice Daily (n = 278)	Lansoprazole, 15 mg Once Daily (n = 276)	Lansoprazole, 30 mg Once Daily (n = 277)
Daytime heartburn				
Days with pain, %	100	88.9	88.9*	88.9*
Average pain severity score per day*	1.86	1.75	1.69	1.67*
Nighttime heartburn				
Days with pain, %	90.0	88.2	87.5	88.9
Average pain severity score per night*	1.63	1.62	1.50	1.55
Antacid use				
Days used, %	87.5	87.5	87.5	87.5
Average No. of tablets per day	3.91	3.67	3.29*	3.60*

*Statistically significant ($P \leq .05$) vs placebo. Pain severity (range, 0-3) was scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

SYMPTOM RELIEF

Patients in the lansoprazole, 15 mg, treatment group recorded significantly ($P < .001$) fewer days and nights with heartburn, less severe daytime and nighttime heartburn, fewer days of antacid use, and fewer antacid tablets used per day during the first 4 weeks of treatment and during the entire 8-week treatment period compared with patients in the ranitidine group (**Table 3**). During the first 4 weeks of treatment and the entire 8-week treatment period, patients treated with lansoprazole, 30 mg, recorded significantly ($P \leq .04$) fewer days and nights with heartburn, less severe daytime and nighttime heartburn, fewer days of antacid use, and fewer antacid

tablets used per day compared with patients treated with ranitidine.

No statistically significant differences in the percentage of days or nights with heartburn, the average severity of daytime or nighttime heartburn pain, the percentage of days that antacids were used, or the number of tablets taken per day were observed between the lansoprazole, 15 mg once daily, and lansoprazole, 30 mg once daily, treatment groups during the first 4 weeks of the study or during the entire 8-week treatment period.

Thirty-seven percent of patients treated with lansoprazole, 15 mg, and 35% of those treated with lansoprazole, 30 mg, were symptom-free for at least 80% of

Table 3. Summary of Median Diary Data at Weeks 0-4 and 0-8*

Variable	Ranitidine, 150 mg Twice Daily (n = 278)		Lansoprazole, 15 mg Once Daily (n = 276)		Lansoprazole, 30 mg Once Daily (n = 277)	
	Weeks 0-4	Weeks 0-8	Weeks 0-4	Weeks 0-8	Weeks 0-4	Weeks 0-8
Daytime heartburn						
Days with pain, % (25%, 75% quartiles)	43 (18, 82)	35 (14, 70)	29† (7, 64)	25† (6, 54)	32‡ (7, 71)	25‡ (5, 63)
Average pain severity score per day§ (25%, 75% quartiles)	0.64 (0.21, 1.14)	0.53 (0.17, 1.02)	0.36† (0.07, 0.89)	0.32† (0.07, 0.75)	0.39‡ (0.11, 1.0)	0.31† (0.07, 0.90)
Nighttime heartburn						
Days with pain, % (25%, 75% quartiles)	32 (11, 64)	25 (9, 60)	18† (4, 57)	16† (3, 45)	25 (4, 57)	19 (5, 50)
Average pain severity score per night§ (25%, 75% quartiles)	0.46 (0.14, 1.0)	0.36 (0.12, 0.86)	0.25† (0.04, 0.81)	0.21† (0.04, 0.64)	0.29‡ (0.07, 0.88)	0.28‡ (0.05, 0.70)
Antacid use						
Days used, % (25%, 75% quartiles)	32 (14, 68)	28 (12, 62)	18† (4, 50)	17† (4, 43)	21 (4, 68)	20‡ (4, 56)
Average No. of tablets per day (25%, 75% quartiles)	0.82 (0.29, 2.39)	0.78 (0.23, 1.82)	0.46† (0.07, 1.44)	0.43† (0.08, 1.21)	0.59 (0.07, 2.16)	0.45 (0.07, 1.89)

*Weeks 0-4 indicates the first 4 weeks of treatment; weeks 0-8, the entire 8 weeks of treatment.

†Statistically significant at $P \leq .001$ vs ranitidine therapy.

‡Statistically significant at $P \leq .01$ vs ranitidine therapy.

§Pain severity (range, 0-3) was scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

||Statistically significant at $P \leq .05$ vs ranitidine therapy.

their treatment days compared with 23% of patients treated with ranitidine.

Patients treated with either dosage of lansoprazole reported significantly lower average daytime and nighttime heartburn severity compared with those receiving ranitidine or placebo. During the first 4 weeks, the median of the average daytime heartburn severity score was 0.64 for patients treated with ranitidine vs 0.36 for patients treated with lansoprazole, 15 mg once daily, and 0.39 for patients treated with lansoprazole, 30 mg once daily ($P \leq .002$). During the entire 8-week treatment period, the median of the average daytime heartburn severity score for patients treated with ranitidine was 0.53, which was significantly ($P \leq .001$) higher than the scores for those treated with lansoprazole, 15 mg (0.32), and lansoprazole, 30 mg, (0.31). The median of the average nighttime heartburn severity score at 4 weeks was 0.46 for patients treated with ranitidine vs 0.25 and 0.29 for patients treated with lansoprazole, 15 and 30 mg, respectively ($P \leq .006$). These findings were similar to those during the 8-week treatment period: patients treated with ranitidine reported an average nighttime heartburn severity of 0.36 vs 0.21 and 0.28 for patients treated with lansoprazole, 15 and 30 mg, respectively ($P \leq .006$).

Patients treated with ranitidine reported a significantly higher percentage of days that they ingested antacids and a significantly higher average number of antacid tablets ingested per day compared with those who received either dosage of lansoprazole. After 4 and 8 weeks of treatment, patients treated with ranitidine reported significantly higher percentages of days (median, 32.1% and 28.5% of days, respectively) using antacids than patients treated with lansoprazole, 15 mg (median, 17.9% and 16.7% of days, respectively), and lansoprazole, 30

mg (median, 21.4% and 19.6% of days, respectively) ($P \leq .01$). At weeks 4 and 8, patients treated with ranitidine reported significantly ($P \leq .04$) higher numbers of antacid tablets used per day (median, 0.82 and 0.78, respectively) compared with patients treated with lansoprazole, 15 mg (median, 0.46 and 0.43, respectively), and lansoprazole, 30 mg (median, 0.59 and 0.45, respectively).

The frequency of antacid use is associated with the frequency of days or nights with heartburn across all treatment groups. Between 86% and 98% of days of Gelusil use coincided with the presence of heartburn symptoms across all treatment groups, with a higher percentage occurring in the placebo group and similar percentages occurring among the active treatment groups.

When comparisons were made with the placebo group, patients treated with lansoprazole, 15 or 30 mg once daily, also reported both significantly lower percentages of days and nights with heartburn and significantly lower severity scores for both daytime and nighttime heartburn, as well as less antacid usage.

Daily diary data analyses, controlling for individual influential factors, such as baseline heartburn severity, baseline *H pylori* status, age, sex, race, and tobacco, alcohol, and caffeine consumption, and their effect on active treatment group differences, were comparable with overall diary results. Treatment with either dosage of lansoprazole was associated with significant ($P \leq .05$) decreases in heartburn frequency and severity compared with ranitidine treatment, 150 mg twice daily, or placebo.

Multiple linear regression analysis of diary data for factors (ie, treatment, baseline heartburn severity, *H pylori* status, age, race, and lifestyle) that might significantly influence symptom relief revealed that patients with

severe heartburn at baseline and patients who were non-drinkers tended to report more frequent and more severe heartburn during the 8-week treatment period compared with those with moderate heartburn at baseline and patients who were drinkers, respectively. Diary analyses revealed that lansoprazole therapy, 15 and 30 mg, was superior to ranitidine therapy in relieving day and night heartburn when controlling for both baseline heartburn severity and alcohol use.

SAFETY

The incidence of possible or probable treatment-related adverse reactions was comparable among the treatment groups: 14% (41/284) in the lansoprazole therapy, 15 mg once daily, group; 17% (50/288) in the lansoprazole therapy, 30 mg once daily, group; 17% (49/283) in the ranitidine therapy, 150 mg twice daily, group; and 13% (9/70) in the placebo group experienced an event that was considered to be possibly or probably treatment related. Three severe adverse events (hematemesis, abdominal pain, and headache, 1 each in the ranitidine, 150 mg twice daily, lansoprazole, 15 mg once daily, and lansoprazole, 30 mg once daily, treatment groups, respectively) were considered to be possibly treatment related. Abdominal pain and diarrhea were the most commonly reported treatment-related adverse events. The majority of all treatment-emergent adverse events were mild to moderate in severity among all treatment groups. No clinically significant differences were noted between treatment groups in the analysis of laboratory, physical examination, and vital sign data.

COMMENT

The results of these 2 large, multicenter, US studies indicate that once-daily treatment with a proton pump inhibitor (lansoprazole at a dosage of either 15 or 30 mg) is significantly more effective than twice-daily administration of ranitidine in controlling the incidence of daytime and nighttime heartburn. In addition, treatment with lansoprazole, 15 or 30 mg, significantly decreased the severity of daytime and nighttime heartburn compared with treatment with ranitidine or placebo. Not surprisingly, patients treated with ranitidine and placebo consumed higher amounts of antacids on more days than patients treated with either dosage of lansoprazole. Of interest, when we controlled for other factors, such as *H pylori* status and baseline heartburn severity, that may affect symptom response, significantly higher percentages of patients treated with lansoprazole reported daytime and nighttime heartburn relief and reduced symptom severity compared with those treated with ranitidine. While the results observed in this study are consistent with prior studies comparing proton pump inhibitor therapy with H2RA therapy in patients with milder forms of reflux disease,^{9,18,19} one limitation to this study may be the rate (approximately 10%) of premature patient withdrawals, which may have resulted in patient selection bias.

Gastroesophageal reflux disease affects a substantial proportion of the adult population,² with many of these

individuals seeking symptom relief with over-the-counter antacid preparations and, more recently, with over-the-counter H2RAs. However, studies have found that these over-the-counter formulations of H2RAs provide at best partial relief, with complete relief occurring in only 15% of patients.²⁰

The widespread availability and direct-to-consumer advertising of over-the-counter antireflux agents have significantly altered the traditional "step up" GERD treatment protocol. A substantial proportion of patients with reflux who currently present for medical consultation have already tried and failed the traditional "first steps" of GERD management (ie, antacid preparations, H2RAs).^{20,21} While it is likely that these patients have not progressed to complications, such as erosions or stricture, their failure to respond to H2RA therapy suggests that they require more effective antisecretory therapy.

Several studies, including meta-analyses, have confirmed that proton pump inhibitor therapy is more effective in raising and maintaining intragastric pH levels above 4 for longer durations compared with H2RA therapy.^{10,11,22-27} In a study by Bell and colleagues,²² treatment with a proton pump inhibitor maintained intragastric pH above 4.00 for between 15 and 21 hours a day compared with approximately 8 hours daily with treatment with an H2RA.²²

By virtue of its potent and long-lasting effects on 24-hour intragastric pH and its ability to maintain pH above 4.00 for extended periods, proton pump inhibitor therapy effectively relieves the symptoms of reflux even in cases of mild disease.^{7,18} Similar to the findings of this study, other investigators have also found that the percentages of patients who experienced relief of their symptoms, including pain, are higher among those treated with a proton pump inhibitor compared with those treated with an H2RA.^{9,19}

Controlling reflux symptoms not only improves a patient's quality of life but may influence the development of gastroesophageal adenocarcinoma. According to a recent epidemiologic study, the more frequent, more severe, and longer lasting the symptoms of gastroesophageal reflux, the greater the risk of developing gastroesophageal adenocarcinoma.²⁸ Compared with those without reflux symptoms, individuals with recurrent reflux symptoms had an odds ratio of 7.7 (95% confidence interval, 5.2-11.4) for developing gastroesophageal adenocarcinoma. This odds ratio increased to 43.5 (95% confidence interval, 18.3-103.5) among individuals with longstanding and severe symptoms of reflux.

In addition to providing greater symptomatic relief, it has been suggested that the empiric use of proton pump inhibitors is a cost-effective approach to the management of these patients.^{29,30} While it is not surprising that empiric treatment of patients with GERD using a proton pump inhibitor is more cost-effective than endoscopy, recent findings suggest that the use of a proton pump inhibitor is only marginally more costly than the use of an H2RA, while being significantly more effective at relieving symptoms,³¹ maintaining symptomatic remission in those with mild reflux,³² and improving quality of life.²⁹ In a study of 685 patients with suspected GERD who were randomized to receive

either omeprazole or ranitidine, significantly more patients treated with omeprazole were heartburn-free at 4, 8, 12, and 16 weeks compared with those treated with ranitidine.³¹ The overall cost of care during these 16 weeks was only \$23 higher for those treated with omeprazole compared with those treated with ranitidine, primarily as a result of a reduced number of endoscopies being performed.

In summary, lansoprazole therapy at a dosage of either 15 or 30 mg once daily was significantly more effective than ranitidine therapy and placebo in reducing the percentage of days and nights with heartburn, the severity of heartburn, as well as the use of and need for anti-acid therapy among patients with nonerosive esophagitis. These data suggest that lansoprazole and other proton pump inhibitors may be the preferred treatment for any patients with reflux disease for whom treatment with lifestyle modifications and over-the-counter H2RAs fails.

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