

Efficacy and Cost Effectiveness of Lansoprazole Versus Omeprazole in Maintenance Treatment of Symptomatic Gastroesophageal Reflux Disease

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Abstract

Objective: To determine the dosing equivalents and cost effectiveness of lansoprazole versus omeprazole in maintenance therapy of gastroesophageal reflux disease (GERD).

Study Design: Single-blind, randomized, crossover study.

Patients and Methods: After completing a 1-week washout period, 27 outpatients (mean age, 66 years) with documented GERD were randomly assigned to receive omeprazole 20 mg or lansoprazole 15 mg daily for 2 weeks. The dosages were then increased to omeprazole 40 mg or lansoprazole 30 mg daily for an additional 2 weeks. All patients completed a second 1-week washout period before crossing over to the alternate agent. Patients recorded GERD-related symptoms (heartburn, chest pain, and regurgitation) daily in a diary. The total symptom score (the sum of the 3 individual symptom scores) were compared for all treatments. Cost effectiveness was evaluated by determining the cost per percent reduction in the total symptom score.

Results: All treatment groups had significant reductions from baseline in the total symptom score

($P < 0.01$). No significant difference was seen between lansoprazole 15-mg and omeprazole 20-mg groups or the the lansoprazole 30-mg and omeprazole 40-mg groups. Lansoprazole 15 mg was found to be as effective as omeprazole 40 mg and omeprazole 20 mg was as effective as lansoprazole 30 mg. The average cost per percent reduction in total symptom score was \$0.03 for the lansoprazole 15-mg, lansoprazole 30-mg, and omeprazole 20-mg doses and \$0.05 for the omeprazole 40-mg dose.

Conclusion: Lansoprazole is as effective as omeprazole in providing symptomatic relief of GERD. Based on acquisition cost, lansoprazole is more cost effective than omeprazole.

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Many patients with gastroesophageal reflux disease (GERD) require medication for relief of symptoms. Agents such as antacids, alginate acid, and sucralfate provide symptomatic relief in patients with mild to moderate symptoms. Although cisapride and the H₂-antagonists (ranitidine, cimetidine, nizatidine, and famotidine) are effective for relieving heartburn pain and healing mild to moderate esophagitis, the proton pump inhibitors (omeprazole and lansoprazole) are currently the most effective agents for relieving GERD symptoms and healing esophageal lesions.¹⁻³ Proton pump inhibitors are often prescribed for patients who do not respond adequately to H₂-antagonists.⁴

Omeprazole and lansoprazole decrease gastric acid secretion over a 24-hour period by binding irreversibly to the H⁺/K⁺ ATPase pump at the surface of

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the parietal cell. The acid-suppressive effects of lansoprazole 30-mg, omeprazole 20-mg, and famotidine 20-mg were measured in 10 healthy volunteers with no history of gastrointestinal problems using 24-hour intragastric pH monitoring. Omeprazole and lansoprazole were more effective at inhibiting daytime and nocturnal acid secretion than was famotidine, an H₂-antagonist.⁵

Because patients with GERD have a high rate of relapse within 1 year after discontinuing drug therapy, maintenance treatment is highly recommended. Five therapies (ranitidine, cisapride, omeprazole, ranitidine plus cisapride, and omeprazole plus cisapride) were compared in the maintenance treatment of reflux esophagitis. Omeprazole alone or in combination with cisapride was more effective than ranitidine, cisapride, or the combination of ranitidine and cisapride.⁶

Dosing equivalence has been evaluated in a number of studies. In one study,⁷ lansoprazole 30-mg and omeprazole 20-mg were more effective than lansoprazole 15-mg in healing esophageal lesions in patients with erosive reflux esophagitis. In addition, lansoprazole 30-mg provided greater symptomatic relief than did lansoprazole 15-mg or omeprazole 20-mg during the early treatment period. In another study,⁴ lansoprazole 30-mg provided greater symptomatic relief in reflux esophagitis than did omeprazole 20-mg during the first week of the study.

Before 1997, omeprazole was the only proton-pump inhibitor on the formulary at the Veterans Affairs San Diego Healthcare System. Lansoprazole replaced omeprazole on the VAMC national formulary in January 1997. At that time, no published studies had examined the relative dosing equivalents and cost effectiveness of lansoprazole versus omeprazole in the maintenance treatment of GERD. Consequently, our goal in conducting this study was to compare the dosing equivalents and cost effectiveness of low and high doses of lansoprazole and omeprazole.

... PATIENTS AND METHODS ...

Patients were eligible for the study if they had a confirmed diagnosis of chronic GERD based on clinical presentation or results of invasive procedures such as endoscopy, were currently being seen in a gastrointestinal or general medicine clinic, and were currently receiving omeprazole for maintenance treatment of GERD. Patients taking phenytoin, warfarin, or diazepam were excluded because omeprazole inhibits the metabolism of these agents. Patients receiving theophylline were excluded as well because concomitant use of lansoprazole can increase the clearance of theophylline. Also excluded were patients prescribed cisapride concomitantly with omeprazole to control symptoms of GERD and those with a documented diagnosis of esophageal stricture, primary esophageal motility disorder, or a confirmed malignancy. The University of California at San Diego Investigation Review Board and the Veterans Affairs San Diego Investigation Review Board approved the research protocol. Each patient provided written consent before enrollment.

Medication was administered using the randomized, crossover design shown in Figure 1. Because of limited resources, we used a single-blind design. Patients were randomized into 2 groups using a random number chart. All patients completed a 1-week washout period before initial treatment to determine their baseline GERD symptoms. During the washout period, patients were allowed to use Extra Strength Maalox® (Ciba Self-Medication, Inc., Woodbridge, NJ) as needed for symptomatic relief. Group A received omeprazole 20-mg once daily for 2 weeks then omeprazole 40-mg once daily for an additional 2 weeks. Group B received lansoprazole 15-mg once daily for 2 weeks then lansoprazole 30-mg once daily for an additional 2 weeks. After this 4-week treatment period, patients again completed a 1-week washout period before switching to the alternate study drug. Extra Strength Maalox® was permitted during this washout as well.

Figure 1. Study Design

	Week 1	Weeks 2 and 3	Weeks 4 and 5	Week 6	Weeks 7 and 8	Weeks 9 and 10
Group A	Washout	Omeprazole 20 mg	Omeprazole 40 mg	Washout	Lansoprazole 15 mg	Lansoprazole 30 mg
Group B	Washout	Lansoprazole 15 mg	Lansoprazole 30 mg	Washout	Omeprazole 20 mg	Omeprazole 40 mg

The omeprazole 20-mg capsules (Astra Merck, Wayne, PA) and lansoprazole 15-mg capsules (TAP Pharmaceuticals Inc., Deerfield, IL) were repackaged in a blue gelatin capsule shell to prevent patients from knowing which medication they were receiving.

We used the Vigneri symptom assessment diary to assess GERD symptoms.⁶ Patients were given the diary and asked to record daily the severity and frequency of their GERD symptoms (heartburn, chest pain, and regurgitation). We called each patient weekly to gather data on changes in symptoms. Because we did not include a pill count as part of the study, patients were asked about compliance during the call. Patients also were monitored (via diary entries and phone follow-up) for adverse effects, including diarrhea, abdominal pain, nausea, vomiting, constipation, flatulence, and rash.

The severity of symptoms was assessed as follows: grade 0 = no symptoms, grade 1 = mild symptoms, grade 2 = moderate symptoms with mild interference with lifestyle and sleep, and grade 3 = severe symptoms with interference with lifestyle and sleep. The frequency of symptoms was assessed as follows: grade 0 = no symptoms, grade 1 = less than 2 days a week, grade 2 = 2 to 4 days a week, and grade 3 = more than 4 days a week. We calculated a score for each symptom and a total symptom score. To calculate the individual symptom score, we multiplied the severity grade by the frequency grade (range, 0-9). To calculate the total symptom score, we summed each of the 3 individual symptom scores (range, 0-27).

Although no dietary restrictions were prescribed for patients enrolled in the study, they were educated about nonpharmacologic means of preventing GERD symptoms (eg, decreasing fat and caffeine intake, avoiding chocolate and peppermint, stopping tobacco use, and elevating the head of their bed).^{8,9} Because more than 50% of patients at our medical center take drugs that can aggravate GERD symptoms (eg, anticholinergic agents, β -blockers, and calcium channel blockers), we thought it appropriate to include patients taking such medications in our study since they served as their own control.

We evaluated the cost effectiveness of lansoprazole and omeprazole by determining the cost per percent reduction in the total symptom score. Hospitalizations and time lost from work were not assessed. At the time we conducted the study, the acquisition cost per capsule for omeprazole 20 mg was \$1.67 and for lansoprazole 15 mg and 30 mg cost per capsule was \$1.50.

Statistical Analysis

Assuming that a 40% reduction in the total symptom score from baseline would be clinically significant using an α value of 0.05 and a β value of 0.20, we needed a sample size of 10 patients to detect a statistically significant difference between the 4 treatment groups (assuming a baseline total symptom score of 14 and standard deviation \pm 9). If we assumed that a 25% difference between the effects of active drug or different doses would be clinically significant using an α of 0.05 and a β of 0.20, the required sample size would be 25 patients.

We compared the 4 treatment groups using Friedman's analysis of variance, a nonparametric test for related measures. Wilcoxon's signed-rank test for paired data was used as a post-hoc test with statistical significance set at $P < .001$ to decrease the effect of multiple comparisons. All statistical tests were two-tailed and considered significant when $P < .05$. We used the SPSS statistical package for our analyses.

Power analysis revealed that 459 patients would have been needed to detect a difference between the low-dose omeprazole and low-dose lansoprazole groups.

... RESULTS ...

We recruited 45 patients from January through May 1997. Sixteen patients withdrew from the study because of severe GERD symptoms during the initial washout period. One patient was a resident of a board-and-care facility that was unwilling to discontinue the study medication. One patient was withdrawn from the study because of noncompliance and another because of hospitalization. Twenty-seven patients (26 men, 1 woman) with a mean age of 66 years (range, 27 to 84 years) successfully completed the study. Fourteen of these patients were randomly assigned to group A and 13 to group B.

Most patients were older men (\geq 55 years) (Table 1). Thirty-seven percent of patients routinely drank coffee, 15% routinely used tobacco, and 15% routinely drank alcoholic beverages. Fifty-nine percent of patients took medications thought to worsen GERD symptoms; use of these medications remained stable throughout the study period. We did not assess changes in coffee, tobacco, or alcohol consumption. Twenty-four patients (89%) reported mild symptoms during washout period, which resulted in mean total symptom scores of 9.2 for the omeprazole group and 6.9 for the lansoprazole group.

Table 1. Patient Characteristics at Baseline (n = 27)

Sex	26m/1f
Age (mean) (y)	66 ± 9.3
Weight (mean) (kg)	80 ± 11.2
Tobacco (n) (%)	4 (15)
Alcohol* (n) (%)	4 (15)
Coffee (n) (%)	10 (37)
Medications that could exacerbate GERD [†] (n) (%)	16 (59)
Confirmed diagnosis by endoscopy (n) (%)	9 (33)

GERD = gastroesophageal reflux disease.

*≥ 1 ounce of alcohol per day.

[†]Includes anticholinergics, β-blockers, and theophylline.

Eighty-six percent of patients in the omeprazole 20-mg group (12/14) and 92% of patients in the lansoprazole 15-mg group (12/13) reported symptomatic relief with the low dose. The total symptom score at baseline was not significantly different in the omeprazole and lansoprazole groups (mean ± SD, 9.2 ± 6.4 and 6.9 ± 5.7, respectively; $P = .072$, Wilcoxon signed-rank test). The total symptom score decreased significantly from baseline in each of the treatment arms (omeprazole 20 mg, omeprazole 40 mg, lansoprazole 15 mg, and lansoprazole 30 mg) ($P < .01$, Friedman's ANOVA). Omeprazole 20 mg and 40 mg decreased the total symptom score from baseline by 57% ($P = .0007$) and 66% ($P = .0002$), respectively (Figure 2). Mean reduction in total symptom score (TSS) for omeprazole 20 mg and 40 mg daily were 5.2 and 6.0 respectively, representing a 57% ($P = .0007$) and 65% ($P = .0002$) reduction in TSS from baseline. Lansoprazole 15 mg and 30 mg decreased the total symptom score from baseline by 48% ($P = .0029$) and 49% ($P = .0023$), respectively.

Mean reduction in total symptom scores for lansoprazole 15 mg and 30 mg daily were 3.3 and 3.4 representing a 48% ($P = .0029$) and 49% ($P = .0023$) reduction in TSS from baseline. Symptom scores for heartburn, chest pain, and regurgitation were significantly decreased from baseline in all 4 treatment arms ($P < .01$) (Figures 3-5). There were no significant differences between the change in TSS from baseline between the lansoprazole 15-mg and omeprazole 20-mg groups ($P = .54$) or between the lansoprazole 30-mg and omeprazole 40-mg groups ($P = .76$). No statistical difference was detected between omeprazole 20-mg and omeprazole 40-mg ($P = .22$) groups; lansoprazole 15 mg and lansoprazole 30 mg ($P = .51$); omeprazole 20 mg and lansoprazole 30 mg ($P = .68$), or lansoprazole 15 mg and omeprazole 40 mg ($P = .91$).

The average cost per percent reduction in total symptom score was \$0.03 in the lansoprazole 15-mg, lansoprazole 20-mg, and omeprazole 20-mg groups and \$0.05 in the omeprazole 40-mg group (Table 2)

Three patients reported a total of 5 adverse events; diarrhea (3 cases) and nausea (2 cases) were the most frequently reported. All adverse events were mild and all were associated with lansoprazole. No patient withdrew from the study because of adverse events.

Figure 2. Mean Total Symptom Scores

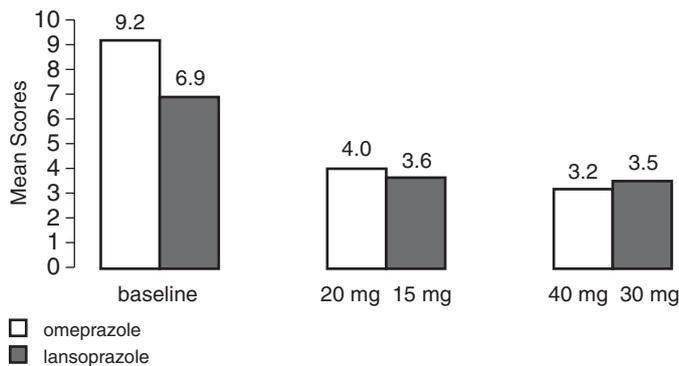
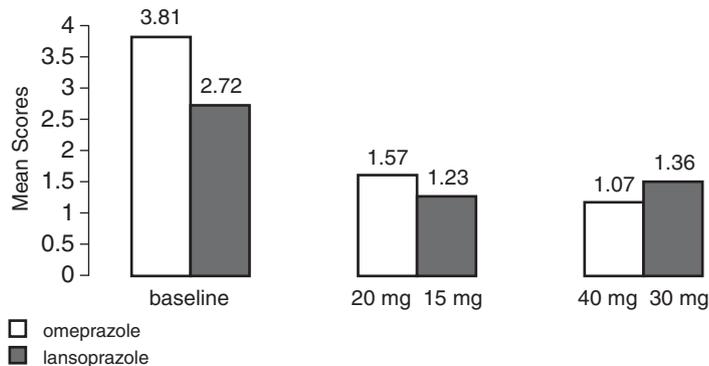


Figure 3. Mean Heartburn Symptom Scores



... DISCUSSION ...

Antacids provide symptomatic relief of GERD but do not promote healing of esophageal erosions. Several studies have shown that healing of esophageal erosions and improvement of symptoms occur when gastric acid secretion is decreased over a 24-hour period.^{6,12} Although cisapride and H₂-antagonists are effective in relieving heartburn and healing mild to moderate esophagitis, proton pump inhibitors are currently the most effective agents for relieving GERD symptoms and healing esophageal erosions.¹²⁻¹⁵

Proton pump inhibitors often account for a large portion of an institution's drug budget. Before conducting this study, we found it difficult to determine which proton pump inhibitor to place on the formulary given the limited number of published trials comparing the dosing equivalents of lansoprazole and omeprazole.

Pharmacy and therapeutics committees must focus on cost effectiveness in addition to safety, efficacy, and acquisition cost. Therefore, the cost effectiveness of medications in the same class must be assessed to determine which agent could save the institution money without compromising clinical outcomes. We determined the cost effectiveness of omeprazole and lansoprazole by computing the cost of therapy per percent reduction in the total symptom score. Since no significant difference in reduction of TSS was detected, lansoprazole was found to be more cost effective than omeprazole.

Eighty-nine percent of the patients who successfully completed our study experienced only mild to moderate symptoms of GERD during the washout periods. This could have been because of lifestyle changes or the administration of an antacid during the washout periods, both of which could have lessened symptom severity. Eighty-nine percent of

Figure 4. Mean Chest Pain Symptom Scores

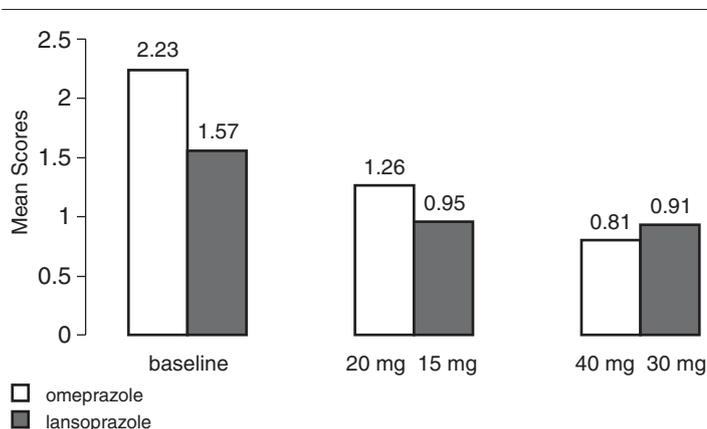


Figure 5. Mean Regurgitation Symptom Scores

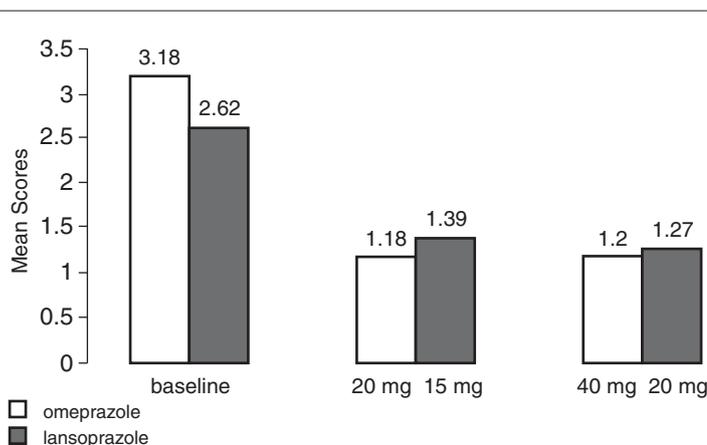


Table 2. Cost-Effective Analysis

Drug	Percent Reduction in Total Symptom Score	*Cost (\$)	Cost (\$)/Percent Reduction
Lansoprazole 15 mg	48	1.50	0.031
Lansoprazole 30 mg	49	1.50	0.031
Omeprazole 20 mg	57	1.67	0.029
Omeprazole 40 mg	66	3.34	0.051

*VA acquisition cost per capsule.

patients in the study experience symptomatic relief and did not require an increase in dose. However, because the dosing equivalents of omeprazole and lansoprazole were unknown at the time of the study, we used low and high doses of each agent in an attempt to determine dosing equivalents.

The most common side effects associated with omeprazole and lansoprazole include headache, diarrhea, nausea, and rash.^{10,11} Three patients reported a total of 5 adverse events during our study. Both study medications were well tolerated. Omeprazole caused no reported adverse effects, but lansoprazole caused mild diarrhea and nausea. However, these adverse events did not require a change in dose or any additional treatment.

Other investigators have reported greater symptomatic relief with lansoprazole 30-mg than with omeprazole 20-mg or lansoprazole 15-mg early in the treatment period.^{4,7} We found no significant difference between any of the treatment arms. This may be because of no difference between the drugs, no added benefit at higher doses, or our small sample size.

Although lansoprazole and omeprazole have a plasma half-life of 0.5 to 1.5 hours, the antisecretory effect of these agents can last up to 72 hours because of prolonged inhibition of the parietal H⁺/K⁺ ATPase enzyme. For this reason, we included a 1-week washout period in our study design before patients switched to the alternate agent. The difference between the 2 baseline periods was not statistically significant ($P = .072$). This may be due to a carryover effect in the lansoprazole treatment arm.

One limitation of our study was that overall patient satisfaction and the ability to convert large numbers of patients from one agent to another were not assessed. It is quite possible that patients can be successfully switched from omeprazole to lansoprazole and that institutions may realize acquisition savings as a result. However, these acquisition savings must be weighed against the risk of decreased patient satisfaction and the risk of increased utilization of other healthcare resources, such as antacids, promotility agents, and additional clinic visits.

In conclusion, lansoprazole and omeprazole significantly decreased total symptom scores from baseline. We found no significant difference in efficacy between omeprazole 20 mg and lansoprazole 30 mg; lansoprazole 15 mg and omeprazole 40 mg; omeprazole 20 mg and omeprazole 40 mg; or lansoprazole 15 mg and lansoprazole 30 mg at acid suppressive doses. There was no significant difference

in symptomatic relief between the 4 treatment groups. Omeprazole and lansoprazole are equally effective agents in treatment of mild to moderate symptomatic GERD. Lansoprazole, however, may offer an advantage over omeprazole due to lower cost and less potential for drug interactions.

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