THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2003 by Am. Coll. of Gastroenterology
Published by Elsevier Inc.

Vol. 98, No. 12, 2003
ISSN 0002-9270/03/$30.00
doi:10.1016/j.amjgastroenterol.2003.09.053

Gastric Acid Control With Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study

Philip Miner, Jr., M.D., Philip O. Katz, M.D., Yusong Chen, Ph.D., and Mark Sostek, M.D.

Oklahoma Foundation for Digestive Research, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; Department of Medicine, Graduate Hospital, Philadelphia; and Divisions of Biostatistics and Clinical Research, AstraZeneca, LP, Wilmington, Delaware

OBJECTIVES: Proton pump inhibitors owe their clinical efficacy to their ability to suppress gastric acid production. The objective of this study was to evaluate and compare intragastric pH following standard doses of esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

METHODS: This randomized, open-label, comparative five-way crossover study evaluated the 24-h intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg once daily in 34 *Helicobacter pylori*–negative patients aged 18–60 yr with symptoms of gastroesophageal reflux disease. Patients were randomly assigned to one of five treatment sequences and study drug was taken on 5 consecutive mornings 30 minutes prior to a standardized breakfast. A washout period of at least 10 days separated each treatment phase.

RESULTS: Thirty-four patients provided evaluable data for all five comparators. The mean number of hours of evaluable pH data was ≥23.75 hours. On day 5, intragastric pH was maintained above 4.0 for a mean of 14.0 h with esomeprazole, 12.1 h with rabeprazole, 11.8 h with omeprazole, 11.5 h with lansoprazole, and 10.1 h with pantoprazole ($p \leq 0.001$ for differences between esomeprazole and all other comparators). Esomeprazole also provided a significantly higher percentage of patients with an intragastric pH greater than 4.0 for more than 12 h relative to the other proton pump inhibitors ($p < 0.05$). The frequency of adverse events was similar between treatment groups.

CONCLUSIONS: Esomeprazole at the standard dose of 40 mg once daily provided more effective control of gastric acid at steady state than standard doses of lansoprazole, omeprazole, pantoprazole, and rabeprazole in patients with symptoms of gastroesophageal reflux disease. (Am J Gastroenterol 2003;98:2616–2620. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Proton pump inhibitors (PPIs) owe their clinical efficacy to their ability to inhibit H^+, K^+-adenosine triphosphatase in gastric parietal cells, resulting in suppression of gastric acid secretion (1). The amount of time that intragastric pH is greater than 4.0 is a parameter that is frequently used to evaluate the pharmacodynamics and clinical effects of treatment with PPIs in patients with acid-related diseases (2–5). Moreover, clinical investigations have confirmed that mucosal healing rates in erosive esophagitis can be correlated with the duration for which intragastric pH is maintained above 4.0 (6).

Previously the effects of PPIs on intragastric pH have been investigated in single-comparator studies (2,7). This trial was designed to compare the intragastric acid-suppressive pharmacodynamics of standard doses of the five PPIs currently available in the United States; esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. This study is the first published comparative pharmacodynamic trial to use a 5-way crossover design and provide the same controlled conditions across all treatment groups.

MATERIALS AND METHODS

A randomized, single-center, open-label, multiple-dose, five-way crossover study was conducted at one center in the United States in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the local institutional review board at the University of Oklahoma Health Sciences Center and all patients provided signed informed consent. The randomization scheme was computer generated. A centralized allocation method was used to assign patients to a treatment group. The choice of treatment sequences was determined by balanced Latin square.

Patients

Men and women aged 18–60 yr, who experienced heartburn for an average of at least 2 days per month during the 2 months before screening were eligible for enrollment. For those patients with a history of more frequent heartburn (three or more heartburn episodes per week during the 3 months before study entry), esophagogastroduodenoscopy was performed if no such evaluation had been performed

within 6 months before study entry. Patients with past or present endoscopic evidence of esophageal erosions, ulcer, or any other significant upper GI pathology were excluded from participation. A rapid urease test by gastric biopsy to detect *Helicobacter pylori* was also performed at the time of esophagogastroduodenoscopy. All other patients underwent a $^{13}CO_2$ urea breath test (Meretek, Nashville, TN). Only patients who were *H. pylori* negative were eligible for enrollment.

Women of childbearing potential were required to use acceptable birth control methods. Exclusion criteria were pregnancy, lactation, any clinically significant abnormal laboratory values at entry, or a history of a clinically significant medical disease. In addition, patients were excluded from the trial if they smoked or consumed nicotine-containing products of any kind within 3 months before the first dose of study drug or during the study; if they consumed any alcoholic beverage or an average of more than four cups of coffee or caffeine-containing beverages per day within 1 wk before the first dose of study drug or during the study; or if they required chronic anti-inflammatory doses of aspirin and/or nonsteroidal anti-inflammatory drugs. Patients were also excluded if they had any history of drug or alcohol dependence, multiple drug allergies, or other drug-associated adverse events. Discontinuation of any previous PPI therapy was required at least 10 days before randomization. No antisecretory drugs, including H_2-receptor antagonists (prescription strength), prokinetic drugs, or any other agents known to alter the pharmacokinetics of PPIs were allowed during the study or within 2 wk before entry.

Study Procedures

Each patient received either esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, or rabeprazole 20 mg orally once daily, 30 min before a standardized breakfast for 5 consecutive days during each of the five treatment periods. Each dose of study drug was placed in an opaque envelope and given to the patient by a study coordinator who observed emptying of the study drug into the patient's mouth and swallowing of the dose. Patients were prohibited from examining the study drugs. A standardized breakfast was provided to the patients 30 minutes following each dose of study drug and patients were dismissed from the clinic after they had been observed eating the breakfast. A maximum of six tablets of Gelusil® (Pfizer Inc., Canada) per day was permitted for heartburn rescue therapy as needed, except after midnight on day 4 through the end of each treatment period. Patients were domiciled at the single investigational site during day 5, when 24-h intragastric pH monitoring was conducted and standardized meals provided. Each treatment period was separated by a washout period of $\geq$10 days, during which no PPI was taken. This was considered sufficient to avoid any carryover effects on either gastric acid production or hepatic enzyme activity from the previous drug. The treatment periods were based around a repeated two-week schedule with the study drug being started and stopped, and the pH study being conducted on the same day of the week. If a patient was unable to attend the clinic one week, they came back on the same day the following week resulting in washout periods of 10, 17 or 24 days.

An ambulatory 24-h intragastric pH recording was performed beginning on day 5 of each treatment period. A calibrated microelectrode attached to a Medtronics Digitrapper pH data logger (Medtronics, Minneapolis, MN) was positioned 10 cm below the manometrically located lower esophageal sphincter and used to evaluate intragastric pH every 4 s. Study drug was administered after probe placement on day 5 of each treatment period. All pH traces were blinded and assessed for evaluability by a single gastroenterologist, independent of the principal investigator.

The primary pharmacodynamic endpoint of this study was the amount of a 24-h period that intragastric pH was maintained above 4.0 by each of the study drugs on day 5 of treatment. Twenty-four hour mean pH on day 5 was determined for each treatment group. The percentage of subjects who had more than 12 h of intragastric pH greater than 4.0 on day 5 was also determined.

For the assessment of tolerability, all patients were encouraged to report adverse events spontaneously or in response to general questioning. Routine laboratory screening, which included hematology, clinical chemistry, and urinalysis, was conducted at the screening visit and at the termination of the study and monitored for any clinically significant changes.

Statistical Methods

Pharmacodynamic analyses were performed for evaluable patients who received all doses in each of the five treatment periods, and who, for each treatment phase, had at least 17 h of pH data within the reference range ($>$0.5 to $<$10.0) and not more than one continuous hour outside of this range. The percentage of time and number of hours (of the 24-h interval) with a pH greater than 4.0 on day 5 were analyzed with a mixed model with effects for subject, period, and treatment, in which subject was a random effect. The least square mean and SEM for each treatment was directly calculated. Statistical comparisons were performed with analysis of variance. A similar model was developed to evaluate the percentage of subjects with intragastric pH greater than 4.0 for more than 12 h. The OR for each pair of comparators was calculated, along with the 95% CIs. *P* values were determined with the χ^2 test. Similarly, for each comparison of mean 24-h intragastric pH between esomeprazole and other PPIs, the least square mean, SEM, 95% CIs, and *p* value were determined. A *p* value less than 0.05 was considered significant.

Safety assessments were recorded and tabulated for all patients who received at least one dose of study drug.

Sample Size

It was estimated that 30 evaluable patients would be required to provide 95% overall power to detect a difference

Table 1. Baseline Demographic and Clinical Characteristics (Evaluable Cohort; N = 34)

Characteristic	Value
Gender, n (%)	
Male	8 (23.5)
Female	26 (76.5)
Age (yr)	
Mean (SD)	44.1 (11)
Range	20–62
Race, n (%)	
Caucasian	31 (91.2)
Other	3 (8.8)
Height (cm)	
Mean (SD)	167.6 (8.5)
Range	152.4–188.0
Weight (kg)	
Mean (SD)	83.2 (18.1)
Range	44.5–125.8
Body mass index (kg/m^2)	
Mean (SD)	29.4 (5.1)
Range	19.2–39.5
History of heartburn ≥3 times/wk during the last 3 mo, n (%)	23 (67.6)

of 12.4% between esomeprazole 40 mg once daily and any one of the other four PPI treatments, assuming the within-patient SD to be 10.5 and the significance level to be 0.05. The trial was designed to randomize 45 patients to compensate for an expected 33% dropout rate, or non-evaluable rate due to the complexity of trial methodology and stringent requirements for evaluability.

RESULTS

Forty-five patients were randomized to form the intent-to-treat and safety cohorts. The first patient entered the study on December 4, 2001, and the last patient completed the study on June 23, 2002. Eleven patients were excluded from the evaluable group. Two withdrew consent. Three discontinued because of adverse events. In the remaining six patients, their pH measurements were not evaluable because of miscalibration (one patient), Digitrapper failure (one patient), premature removal of the pH probe (one patient), or a pH outside the reference range for more than 1 continuous

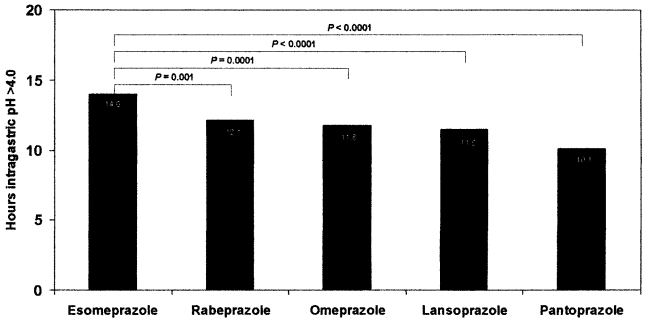

Figure 1. Mean number of hours on day 5 that intragastric pH was >4.0 by treatment group (N = 34).

Table 2. The Mean Number of Hours of pH Data for Each Treatment Group

Treatment	n	Mean (SD); hours	Range; hours
Esomeprazole	34	23.85 (0.09)	23.34–23.86
Lansoprazole	34	23.77 (0.31)	22.25–23.86
Omeprazole	34	23.84 (0.11)	23.27–23.86
Pantoprazole	34	23.86 (0.02)	23.73–23.86
Rabeprazole	34	23.75 (0.59)	20.40–23.86

hour (three patients). Evaluable traces for all five PPIs were required for a patient to be considered in the efficacy analyses.

Table 1 summarizes the baseline demographic and clinical characteristics of the 34 patients in the evaluable cohort. Approximately three quarters of the patients were women, and the majority had a history of three or more episodes of heartburn per week during the 3 months before screening. Of the 136 washout periods (four for each patient), most were 10 days (n = 113), although some were 17 (n = 20) or 24 (n = 3) days. Table 2 summarizes the mean number of hours of evaluable pH data for each treatment group. Of the 170 evaluable traces, although the protocol considered >17 hours of data acceptable, only one trace contained less than 22 hours data. The mean number of hours of pH data for each treatment group ranged between 23.75 and 23.86.

The mean number of hours for each treatment group that intragastric pH was greater than 4.0 on day 5 is shown in Figure 1. Treatment with esomeprazole provided significantly more hours with intragastric pH greater than 4.0, compared with all other PPIs.

The percentage of time on day 5 that intragastric pH was greater than 4.0 and the mean 24-h intragastric pH for each treatment group are shown in Table 3. There was a statistically significant difference between esomeprazole and all of the other PPIs for the percentage of the 24-h period that intragastric pH was greater than 4.0 and for mean pH.

The percentage of patients with intragastric pH greater than 4.0 for more than 12 h is presented in Figure 2. A significantly higher percentage of patients treated with esomeprazole had intragastric pH greater than 4.0 for more than 12 h relative to treatment with all other PPIs. Compar-

Table 3. Percent Time (Least Square Mean) That Intragastric pH Was 4.0 and Mean 24-Hr Intragastric pH on Day 5 by Treatment Group (N = 34)

Treatment	% Time pH > 4.0 (SEM)	Mean pH (SEM)
Esomeprazole 40 mg	58.43* (3.13)	4.04† (0.16)
Rabeprazole 20 mg	50.53 (3.38)	3.70 (0.17)
Omeprazole 20 mg	49.16 (3.38)	3.54 (0.17)
Lansoprazole 30 mg	47.98 (3.26)	3.56 (0.15)
Pantoprazole 40 mg	41.94 (3.19)	3.33 (0.17)

* $p \leq 0.0001$ for comparison of esomeprazole *versus* lansoprazole, omeprazole, and pantoprazole; $p = 0.001$ for comparison between esomeprazole and rabeprazole.

† $p < 0.0001$ for comparison of esomeprazole *versus* lansoprazole, omeprazole, and pantoprazole; $p = 0.003$ for comparison between esomeprazole and rabeprazole.

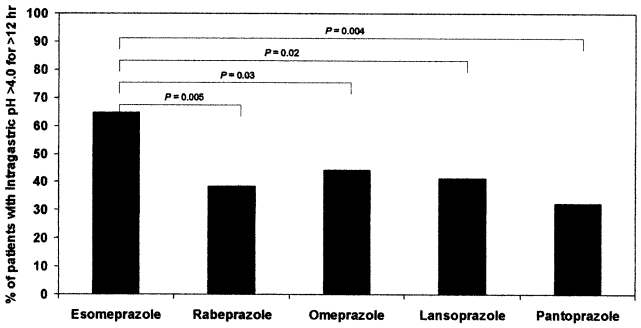

Figure 2. Percent of subjects with intragastric pH >4.0 for >12 hours (N = 34).

isons between the other pairs of PPIs did not reach statistical significance; all showed efficacy comparable to each other for this parameter.

The number and frequency of adverse events, serious adverse events, and discontinuations due to adverse events are presented in Table 4. There were four serious adverse events, none considered treatment-related, but two resulted in study withdrawal. A third patient withdrew because of a nonserious adverse event (nausea). The types of adverse events that were observed were similar to those previously reported and most frequently included headache, nausea, diarrhea, flatulence, or abdominal pain.

DISCUSSION

All five PPIs investigated in our study provided gastric acid suppression (pH>4) for at least 10 hours in a 24 hour period. Esomeprazole (40 mg once daily) provided an intragastric pH greater than 4.0 for a significantly greater amount of a 24-h period at steady state (day 5) compared with standard-dose lansoprazole, omeprazole, pantoprazole, or rabeprazole in patients with symptoms of gastroesophageal reflux disease. Similarly, the percentage of patients with an intragastric pH greater than 4.0 for more than 12 h was significantly greater with esomeprazole relative to the other PPIs. Although the study was not specifically designed to detect differences in this parameter between the other pairs of PPIs, no statistical differences were found. For all efficacy endpoints, the results were numerically lowest with pantoprazole, although statistically the differences were only significant compared with esomeprazole.

Until now, it has been difficult to compare the pharmacodynamic properties of each of these five PPIs directly because previous trial designs involved a single comparator. The five-way crossover study that we performed provided an opportunity for a direct comparison between PPIs. These results support those from the single-comparator studies, which showed that esomeprazole 40 mg provided more effective control of gastric acid than omeprazole 40 mg on days 1 and 5, as measured by the mean percentage of a 24-h period that intragastric pH was greater than 4.0 (2). In other studies using single comparators, standard-dose esomeprazole maintained intragastric pH greater than 4.0 for a longer percentage of a 24-h period at day 5 than did standard doses of lansoprazole, pantoprazole, or rabeprazole (7).

In our study, esomeprazole maintained intragastric pH greater than 4.0 on day 5 for 58.4% of the 24-h period. In other studies, the percentage of a 24-h interval that intragastric pH was greater than 4.0 after 5 days of esomeprazole ranged between 57.7% and 69.8% (2, 7–9) . Although this narrow range might in part be attributable to less interpatient variability, as assessed by the area under the plasma concentration–time curve with esomeprazole compared with omeprazole (8), it also emphasizes the importance of head-to-head comparisons within one and the same study.

There are limitations to this study. Although an open-label design is standard practice for pH studies, this comparative crossover study would ideally have a double-blind methodology. However, introducing a double-blind design would have required over-encapsulation, which could affect dissolution, bioavailability and other pharmacokinetic parameters of the study drugs. We did adopt a "masked dosing" technique that ensured patients were blinded to the study drug they took on any particular occasion.

Although our study did not investigate the effect of the five PPIs on any clinical endpoints, small studies with cimetidine and/or omeprazole have correlated duration and degree of esophageal acid exposure with clinical endpoints such as healing of esophageal erosions (13, 14). Other authors have also suggested that a clear relationship exists between the degree of esophageal acid exposure and healing of erosive esophagitis (6, 15). The more effective gastric acid–suppressive pharmacodynamics of esomeprazole might contribute to its improved clinical efficacy compared with other PPIs. In well-designed clinical trials, esomeprazole 40 mg once daily produced significantly higher rates of

Table 4. Adverse Events and Discontinuations Because of Adverse Events

	Esomeprazole 40 mg (n = 42)	Omeprazole 20 mg (n = 38)	Lansoprazole 30 mg (n = 39)	Pantoprazole 40 mg (n = 41)	Rabeprazole 20 mg (n = 43)
Any AE	16 (38.1)	14 (36.8)	17 (43.6)	23 (56.1)	19 (44.2)
Treatment-related AE	7 (16.7)	7 (18.4)	8 (20.5)	14 (34.1)	6 (14.0)
Serious AE	1 (2.4)	0 (0)	2 (5.1)	0 (0)	1 (2.3)
Discontinuation of study treatment because of AE	2 (4.8)	0 (0)	0 (0)	0 (0)	1 (2.3)

Data are presented as n (%). AE = adverse events.

healing and symptom resolution in patients with erosive esophagitis relative to lansoprazole 30 mg or omeprazole 20 mg once daily (10–12). However, a large well-designed study that investigated the relationship between the pharmacodynamic endpoints we describe and clinical endpoints relevant to GERD would be desirable.

In summary, this randomized, five-way crossover trial demonstrated that standard-dose esomeprazole (40 mg once daily) suppresses intragastric acid production for a greater amount of a 24-h period in patients with symptoms of gastroesophageal reflux disease than do standard doses of other PPIs.

ACKNOWLEDGMENTS

The authors would like to acknowledge Christopher Rains, Karen van Hoeven, and Caroline Spencer for their assistance with manuscript preparation.

Reprint requests and correspondence: Philip Miner, Jr., M.D., Oklahoma Foundation for Digestive Research, University of Oklahoma Health Sciences Center, 711 Stanton L. Young Boulevard, Suite 619, Oklahoma City, OK 73104.

Received May 14, 2003; accepted Sep. 30, 2003.

REFERENCES

1. Sachs G, Shin JM, Briving C, et al. The pharmacology of the gastric acid pump: The H+,K+ ATPase. Annu Rev Pharmacol Toxicol 1995;35:277–305.
2. Rohss K, Hasselgren G, Hedenstrom H. Effect of esomeprazole 40 mg vs omeprazole 40 mg on 24-hour intragastric pH in patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci 2002;47:954–8.
3. Franco MT, Salvia G, Terrin G, et al. Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood. Dig Liver Dis 2000;32:660–6.
4. Katz PO, Hatlebakk JG, Castell DO. Gastric acidity and acid breakthrough with twice-daily omeprazole or lansoprazole. Aliment Pharmacol Ther 2000;14:709–14.
5. Labenz J, Tillenburg B, Peitz U, et al. Efficacy of omeprazole one year after cure of *Helicobacter pylori* infection in duodenal ulcer patients. Am J Gastroenterol 1997;92:576–81.
6. Bell NJ, Burget D, Howden CW, et al. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992;51:59–67.
7. Röhss K, Wilder-Smith C, Claar-Nilsson C, et al. Esomeprazole 40 mg provides more effective acid control than standard doses of all other proton pump inhibitors. Gastroenterology 2001;120(5)(Suppl1):A-418 (abstract 2140).
8. Lind T, Rydberg L, Kyleback A, et al. Esomeprazole provides improved acid control vs omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2000;14:861–7.
9. Katz PO, Castell DO, Chen Y, et al. Esomeprazole 40 mg twice daily maintains intragastric pH $>$ 4 for more than 80% of a 24-hour time period. Am J Gastroenterol 2002;97:S20–1.
10. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002;97:575–83.
11. Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: A randomized controlled trial. Aliment Pharmacol Ther 2000;14:1249–58.
12. Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: A randomized controlled trial. Am J Gastroenterol 2001;96:656–65.
13. Holloway RH, Dent J, Narielvala F, Mackinnon AM. Relation between oesophageal acid exposure and healing in patients with severe reflux oesophagitis. Gut 1996;38:649–54.
14. Dehn TCB, Shepherd HA, Colin-Jones D, Kettlewell MGW, Carroll NJH. Double-blind comparison of omeprazole (40mg od) versus cimetidine (400mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24 h pH monitoring. Gut 1990;31:509–13.
15. Huang JQ, Hunt RH. pH, healing rate and symptom relief in patients with GERD. Yale J Biol Med 1999;72:181–94.