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

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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 ($p < 0.001$ 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 who had 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 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.

**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, SEM, 95% CI, 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
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 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.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Mean (SD); hours</th>
<th>Range: hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 40 mg</td>
<td>34</td>
<td>23.85 (0.09)</td>
<td>23.34–23.86</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>34</td>
<td>23.77 (0.31)</td>
<td>22.25–23.86</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>34</td>
<td>23.84 (0.11)</td>
<td>23.27–23.86</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>34</td>
<td>23.86 (0.02)</td>
<td>23.73–23.86</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>34</td>
<td>23.75 (0.59)</td>
<td>20.40–23.86</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Time pH &gt; 4.0 (SEM)</th>
<th>Mean pH (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 40 mg</td>
<td>58.43* (3.13)</td>
<td>4.04† (0.16)</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>50.53 (3.38)</td>
<td>3.70 (0.17)</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>49.16 (3.38)</td>
<td>3.54 (0.17)</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>47.98 (3.26)</td>
<td>3.56 (0.15)</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>41.94 (3.19)</td>
<td>3.33 (0.17)</td>
</tr>
</tbody>
</table>

* p ≤ 0.0001 for comparison of esomeprazole versus lansoprazole, omeprazole, and pantoprazole; † p = 0.001 for comparison between esomeprazole and rabeprazole.

† p < 0.0003 for comparison between esomeprazole versus lansoprazole, omeprazole, and pantoprazole; p = 0.001 for comparison between esomeprazole and rabeprazole.
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

**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.

**Table 4. Adverse Events and Discontinuations Because of Adverse Events**

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

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.

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