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A comparison of esomeprazole and lansoprazole for control of intragastric pH in patients with symptoms of gastro-oesophageal reflux disease

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SUMMARY

Background: Intragastric acid suppression is the most direct measure of the pharmacodynamic efficacy of proton pump inhibitors, which are the most effective drugs for acid-related diseases.

Aim: To compare the effectiveness of once and twice daily dosing of lansoprazole and esomeprazole in controlling intragastric acidity (target gastric pH > 4.0) over a 24-hour period.

Methods: In an open-label, two-way crossover study, 45 *Helicobacter pylori*-negative patients with gastro-oesophageal reflux disease were randomized to receive one of two regimens: 30 mg lansoprazole or esomeprazole 40 mg once daily. Intragastric pH was assessed by 24-hour pH monitoring on day 5 of each regimen. Dosing was increased to twice daily and pH was reassessed on day 10. Following a 14-day washout, patients were crossed over to the other medication and the dosage regimens and pH assessments were repeated.

Results: Data were analysed from 35 patients who completed all scheduled assessments and had 24-hour monitoring for each end-point. Mean time pH > 4.0 and mean 24-hour pH were highest for esomeprazole 40 mg twice daily, followed by lansoprazole 30 mg twice daily, esomeprazole 40 mg once daily and lansoprazole 30 mg once daily. Esomeprazole 40 mg twice daily provided superior control of intragastric pH compared with either once or twice daily dosing of lansoprazole and once daily dosing of esomeprazole ($P < 0.01$). Esomeprazole 40 mg once daily was comparable with lansoprazole 30 mg twice daily and both were superior to lansoprazole 30 mg once daily ($P < 0.01$).

Conclusions: Response to acid suppression treatment depends on the treatment selected. Esomeprazole 40 mg twice daily provided better control of intragastric pH than all other regimens evaluated. Esomeprazole 40 mg daily, however, was comparable with lansoprazole 30 mg twice daily and superior to lansoprazole 30 mg once daily.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common disorder characterized by heartburn symptoms, acid regurgitation or the presence of oesophageal lesions. The development of these symptoms and mucosal injury in patients with GERD depends on intragastric pH.[1] Proton pump inhibitors (PPIs) are the most effective drugs for acid-related diseases, including GERD, with proven superiority to histamine H_2-receptor antagonists.[2] Proton pump inhibitors suppress gastric acid secretion through the inhibition of H^+/K^+ adenosine triphosphatase in gastric parietal cells.[3] Intragastric acid suppression, measured as the number of hours in a

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24-hour period that intragastric pH is maintained above 4.0, is used to compare the effects of PPIs[4–6] and is correlated with mucosal healing rates in erosive oesophagitis.[7]

Esomeprazole is the S-isomer of omeprazole and the first PPI developed as a single isomer. Esomeprazole has an enhanced pharmacodynamic and pharmacokinetic profile resulting in more effective and longer-lasting inhibition of gastric acid secretion over the 24-hour dosing period[8–10] and is more effective at healing and resolution of heartburn than the racemic omeprazole.[11–13] Intragastric acid is more effectively controlled with the standard dose of esomeprazole (40 mg once daily) than standard doses of all other PPIs, as measured by the percentage of time pH > 4.0 and mean 24-hour pH.[14–17] Furthermore, esomeprazole provides complete heartburn relief in the majority of patients with GERD.[18] Compared with lansoprazole, esomeprazole has been shown to be more effective in resolving heartburn with faster sustained relief and in healing erosive oesophagitis.[19, 20]

The primary objective of this study was to compare the effects of once and twice daily dosing of esomeprazole 40 mg and lansoprazole 30 mg on intragastric pH over a 24-hour period in patients with GERD symptoms. This study uses a novel crossover design to evaluate the effects of once and twice daily dosing of two different PPIs.

PATIENTS AND METHODS

Patients

Men and women aged between 18 and 75 years who were negative for *Helicobacter pylori* (breath test or biopsy within 1 month of study entry) and had a history of heartburn symptoms averaging at least 2 days/month during the last 2 months before screening or a history of GERD documented by endoscopy, pH study or prior response to PPI therapy were eligible for the study. Women were required to not be pregnant or lactating, and those of child-bearing potential had to be surgically sterile or be using an acceptable method of birth control.

Patients were excluded if they had a history of gastrointestinal disease, gastrointestinal surgery or other conditions that may affect absorption or pharmacokinetics of the study drug. In addition, patients were excluded if they required chronic aspirin >325 mg/day, non-steroidal anti-inflammatory drugs or medication that depends on the presence of gastric acid for optimal absorption, such as ketoconazole, iron salts, digoxin or ampicillin esters. Patients treated with prescription-strength H_2-receptor antagonists, prokinetic medications or medications that could alter the pharmacokinetics of PPIs within 2 weeks before the first dose of study drug were excluded.

Patients on pre-existing PPI therapy were required to discontinue treatment at least 10 days before randomization. Those who could not stop their GERD therapy were not permitted to enter the study. Patients with a history of ≥3 heartburn episodes per week before study entry were required to have an oesophagogastroduodenoscopy before randomization to rule out oesophageal erosions, ulcers, oesophageal or gastric neoplasms, Barrett's oesophagus or other upper endoscopic pathology. Patients with significant gastrointestinal pathology were not enrolled.

Patients could not participate in the study if they had a significant clinical illness during the study or within 2 weeks before the first dose of study drug or had a history of a clinically significant medical condition whose treatment may be adversely impacted by participation. Patients who received an investigational drug or used an experimental device within 30 days before screening or donated blood within 8 weeks before screening also were ineligible to participate. Additionally, patients were required to have no abnormal laboratory values that were clinically significant and be within 25% of ideal body weight for their height and frame. Patients who smoked >10 cigarettes per day or used the equivalent nicotine-containing product, consumed more than four cups of coffee or caffeine-containing beverages per day, consumed alcohol within 1 week before or during the study, had a history of drug or alcohol dependence or current abuse, had a history of intolerance to esomeprazole or any other approved PPI or had a history of multiple drug allergies or drug-associated adverse events were excluded.

Study design

A randomized, open-label, single-centre, four-treatment, two-way crossover comparative study assessed the effect of two doses each of esomeprazole and lansoprazole on intragastric pH. Patients were randomized by a computer-generated randomization schedule to receive either lansoprazole 30 mg or esomeprazole 40 mg once daily (30 minutes before a standardized breakfast) for 5 consecutive days (Figure 1). Dosing regimens were then

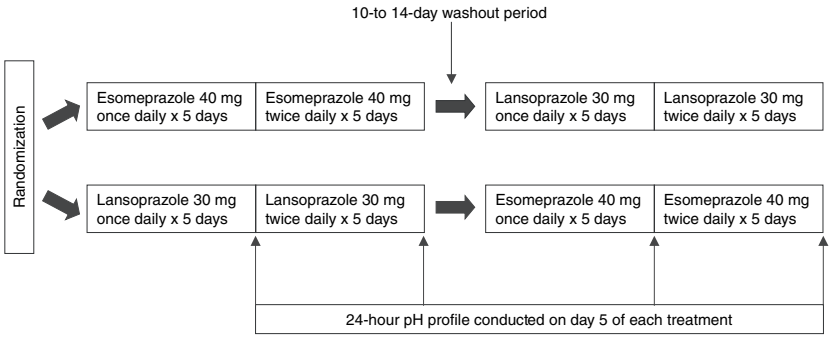

Figure 1. Study design.

increased to twice daily (30 minutes before breakfast and dinner) for an additional 5 consecutive days. The first dose of the first day of each treatment arm was administered in the study clinic. All subsequent doses were taken by the patients at home. Patients were instructed on a standardized diet and were asked to be consistent throughout the study. Following a 10- to 14-day washout, patients were crossed over to the other treatment. An ambulatory 24-hour intragastric pH recording was done on day 5 to day 6 during each treatment period. The pH probe (Medtronics, Minneapolis, MN, USA) was placed 10 cm below the distal border of the manometrically defined lower oesophageal sphincter. After the 24-hour, pH profile was obtained for treatment periods 1 and 3, the pH probe was removed (day 6) and subsequently the first dose of the appropriate study medication was administered to begin the next treatment period. Rescue medication with Gelusil [Warner Lambert Consumer Healthcare (Parke Davis), Morris Plains, NJ, USA] was permitted (maximum of six tablets/day) except after midnight on day 4 and during pH monitoring on days 5 and 6. Patients were ambulatory and outpatients during the 24-hour intragastric pH monitoring. A minimum of 22 hours was chosen as a threshold for acceptable data to be included for analysis. The hours were then extrapolated proportionately to allow for standardized comparisons between each of the treatment arms, based on 24 hours of monitoring.

Statistical analysis

The primary end-point was the percentage of time intragastric pH was >4.0 on day 5 and was analysed using one-way repeated analyses of variance (ANOVA) and Duncan's Multiple Range tests. Six paired comparisons of hours with pH > 4 were made among the four treatments. Assuming a 10% difference in the percentage of time intragastric pH > 4.0 between esomeprazole 40 mg b.d. and lansoprazole 30 mg b.d., 36 patients were needed to provide 90% power to detect this difference at a significance level of 0.05.

Data for each of the four treatments were analysed with the statistical software package SPSS. Each patient received each of the four treatments; therefore, a randomized complete block design was assumed with each patient serving as a block. To determine which treatment differed from the others, the Sidak method of multiple comparisons was invoked to protect against false significances (i.e. Type 1 errors) using an error rate of 0.05.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, US Food and Drug Administration guidance, Good Clinical Practice regulations and Guidelines for the Monitoring of Clinical Investigations. In addition, the study was approved by the Institutional Review Board and each patient provided written informed consent before enrollment.

RESULTS

Study population

Forty-five patients were randomized into the study (Figure 1). Demographic characteristics of the 35 patients who completed all scheduled assessments and 24-hour monitoring for each treatment are summarized in Table 1.

Time pH > 4.0

When treated with esomeprazole 40 mg b.d., patients had a higher average response (number of hours with

Table 1. Demographic characteristics of patients included in analyses

Characteristic	($n = 35$)
Women	
n (%)	22 (63)
Mean age, year (range)	46 (29–71)
White/Black/Asian, *n*	17/4/1
Men	
n (%)	13 (37)
Mean age, year (range)	52 (33–65)
White/Black/Asian, *n*	11/2/0

pH > 4) than with each of the other treatments; the average response with esomeprazole 40 mg daily was higher than with lansoprazole 30 mg daily; and the average response with lansoprazole 30 mg b.d. was higher than with lansoprazole 30 mg once daily (Figure 2).

Mean 24-hour pH

The mean 24-hour pH was significantly higher during treatment with esomeprazole 40 mg once or b.d. when compared with lansoprazole 30 mg once daily ($P < 0.01$ and $P < 0.001$, respectively; Figure 3). Mean 24-hour pH was significantly higher ($P < 0.01$) when patients were treated with esomeprazole 40 mg b.d. than when they were treated with esomeprazole 40 mg once daily; esomeprazole once daily was not significantly different from lansoprazole 30 mg b.d. The mean pH achieved with lansoprazole 30 mg b.d. also was significantly higher than that achieved with lansoprazole 30 mg once daily ($P < 0.001$).

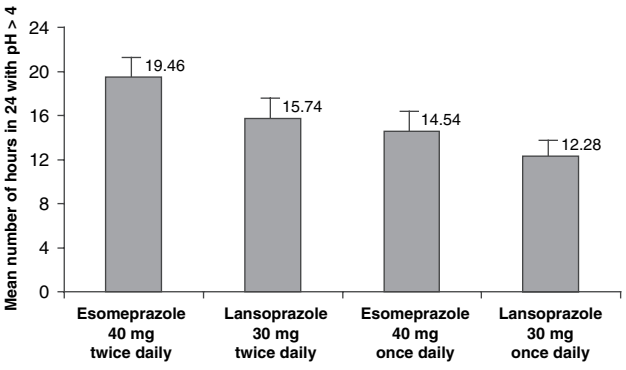

Figure 2. Mean number of hours in a 24-hour period (95% CI) with intragastric pH > 4.0 on day 5 ($n = 35$).

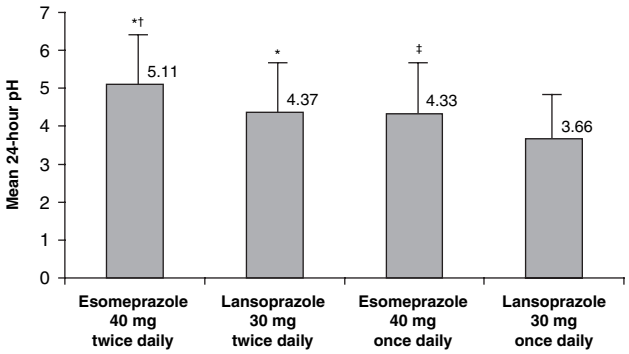

Figure 3. Mean 24-hour intragastric pH on day 5 ($n = 35$). *$P < 0.001$ vs. lansoprazole 30 mg once daily. †$P < 0.01$ vs. esomeprazole 40 mg once daily. ‡$P < 0.01$ vs. lansoprazole 30 mg once daily.

DISCUSSION

The results of this study demonstrate that greater intragastric acid suppression occurs with esomeprazole 40 mg b.d. compared with once daily dosing and is superior to that of lansoprazole 30 mg whether administered once or twice daily. Esomeprazole 40 mg administered once daily results in a greater number of hours with pH > 4 than lansoprazole 30 mg administered once daily and a similar number of hours with pH > 4 compared with lansoprazole 30 mg b.d.

Previous studies have demonstrated that intragastric acid is more effectively controlled with esomeprazole than rabeprazole, omeprazole, lansoprazole and pantoprazole, as measured by the percentage of time pH > 4.0 and mean 24-hour pH.[14–17] In a five-way crossover study, standard-dose esomeprazole also was shown to provide a greater mean number of hours in a 24-hour period with pH above prespecified thresholds (between 2.0 and 6.0) than standard doses of rabeprazole, omeprazole, lansoprazole and pantoprazole.[17]

These results are consistent with those of previous studies comparing standard and escalated doses of esomeprazole, either alone or in comparison with other PPIs. Recently, a randomized, three-way, dose-ranging crossover study of healthy subjects showed that esomeprazole 40 mg b.d. provides significantly greater acid suppression (hours with pH > 4) than esomeprazole 20 mg b.d. or 40 mg once daily [19.2 hours (80.1% of 24-hour period; 95% confidence interval (CI) 74.5–85.7%); 14.2 hours (59.2% of 24-hour period; 95% CI 53.7–64.7); and 17.5 hours (73% of 24-hour period;

95% CI 67.4–78.5), respectively].[21] In a study of patients with Barrett's oesophagus who received three different dosing regimens of esomeprazole (20 mg t.d.s., 40 mg b.d. and 40 mg t.d.s.), all three regimens were shown to provide high levels of intragastric acid suppression.[22] In addition, the number of hours or mean percentage of time in a 24-hour period with intragastric pH > 4.0 increased with increasing esomeprazole dosage, and the 40-mg 3-times-daily regimen provided statistically superior gastric acid suppression compared with the other two regimens ($P < 0.01$).[22] In healthy subjects, standard doses of esomeprazole (40 mg once daily) provided longer and more effective intragastric acid control than both standard and double doses of lansoprazole (30 and 60 mg once daily, respectively).[23] Furthermore, in a comparison of twice daily dosing of esomeprazole 40 mg and pantoprazole 40 mg in healthy subjects, esomeprazole was significantly more effective at controlling intragastric pH.[24]

Suboptimal symptomatic response to PPI therapy may lead the physician to double the PPI dose rather than switch the medications. Besides the superiority of intragastric acid control with esomeprazole treatment shown from the results of previous studies, single-dose esomeprazole also has been shown to control heartburn symptoms as well as double-dose lansoprazole administered once daily in patients with GERD symptoms refractory to lansoprazole 30 mg once daily.[25] Furthermore, switching from a twice daily PPI to once daily esomeprazole is clinically successful and cost-saving.[26] This treatment strategy may be an effective way to manage GERD in patients requiring greater than a single daily dose of PPI to achieve an acceptable level of acid suppression.

Results of this study suggest that greater control of acid secretion depends on the medication selected as well as the dose selected. By extrapolation to clinical practice, these data also suggest that doubling the dosage of lansoprazole may not be a cost-effective strategy to increase intragastric acid suppression given the comparable pH effect achieved with single-dose esomeprazole. Outcome studies to validate this hypothesis are presently under way.

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