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Effect of Esomeprazole 40 mg vs Omeprazole 40 mg on 24-Hour Intragastric pH in Patients with Symptoms of Gastroesophageal Reflux Disease

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Maintenance of intragastric pH $>$ 4 is vital for effective management of gastroesophageal reflux disease (GERD). Esomeprazole 40 mg, the first proton pump inhibitor developed as an optical isomer, demonstrates improved acid inhibition over omeprazole 20 mg. Our aim was to compare esomeprazole 40 mg with omeprazole 40 mg, once-daily, on intragastric acidity in patients with symptoms of GERD. In this open-label, crossover study, 130 patients with symptoms of GERD received esomeprazole 40 mg or omeprazole 40 mg once-daily for five days. The 24-hr intragastric pH was monitored on days 1 and 5 of each treatment period. The mean percentage of the 24-hr period with intragastric pH $>$ 4 was significantly greater ($P < 0.001$) with esomeprazole 40 mg than with omeprazole 40 mg on days 1 (48.6% vs 40.6%) and 5 (68.4% vs 62.0%). Interpatient variability was significantly less with esomeprazole than omeprazole. Esomeprazole was well tolerated. In conclusion, esomeprazole 40 mg provides more effective acid control than twice the standard dose of omeprazole.

KEY WORDS: esomeprazole; omeprazole; gastroesophageal reflux disease; intragastric pH; pharmacodynamics.

Gastric acid is central to the development of mucosal injury and symptoms in gastroesophageal reflux disease (GERD), with 24-hr esophageal pH monitoring suggesting a direct relationship between the degree and duration of esophageal acid exposure and the extent of mucosal injury (1, 2). The proportion of the 24-hr period with intraesophageal pH $<$ 4 increases progressively from endoscopy-negative GERD through the worsening grades of esophagitis (2). Furthermore, pH 4 is generally accepted as the most appropriate threshold for discriminating between normal and pathological reflux (3, 4). Conversely, healing of mucosal injury correlates with the duration of suppression of intragastric acidity at pH $>$ 4 (1). Accordingly, maintenance of intragastric pH $>$ 4 for the greater part of each 24-hr period provides the key to effective management of GERD.

Proton pump inhibitors (PPIs) are well-established agents for the treatment of GERD, and according to recently published US and European guidelines, offer the most effective means of ensuring rapid symptom relief and esophageal healing (5, 6).

It is apparent, however, that although rates of symptom resolution are generally high with PPIs, some PPIs fail to achieve complete resolution of heartburn and other GERD symptoms (7, 8). Indeed, in a large US survey comparing H_2 -receptor antagonists with omeprazole and lansoprazole (9), less

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than one half of patients reported being totally satisfied with their heartburn medication. Thus, despite the high efficacy of PPIs, an opportunity clearly exists to improve clinical outcomes in patients with GERD.

Esomeprazole, the *S* isomer of omeprazole, is the first PPI to be developed as a single optical isomer for the treatment of acid-related disorders. Esomeprazole has higher systemic bioavailability than racemic omeprazole, and when administered at a dose of 40 mg provides more effective and sustained inhibition of 24-hr intragastric acidity than omeprazole 20 mg (10), lansoprazole 30 mg (11), pantoprazole 40 mg (12), or rabeprazole 20 mg (13). Moreover, the greater acid control provided by esomeprazole 40 mg has been shown to translate into improved symptom resolution and mucosal healing when compared with omeprazole 20 mg in patients with erosive esophagitis. (14, 15)

Given the greater efficacy of esomeprazole 40 mg over omeprazole 20 mg, it is also of interest to consider the effects of equal milligram doses of these two PPIs on intragastric pH. As such, this study compares the effect of esomeprazole 40 mg and twice the standard dose of omeprazole (ie, 40 mg) on 24-hr intragastric acidity after both single- and repeated-dose administration in patients with symptoms of GERD.

MATERIALS AND METHODS

Patients. Male and female patients >20 years of age with symptoms of GERD, experiencing significant symptoms (heartburn and/or acid regurgitation) on at least two days per week during the last two months, were eligible for study inclusion. Patients were required to be *Helicobacter pylori*-negative, as determined by a [^{13}C]urea breath test. The main exclusion criteria were symptoms indicative of complications of GERD (eg, melena, hematemesis), primary esophageal motility disorder, or previous gastric surgery and any pharmacotherapy for GERD within the previous two weeks. Patients with a history of drug addiction and/or alcohol abuse, moderate to heavy smoking (>10 cigarettes/day) or other nicotine use, and those with significant concomitant disease were also excluded from enrollment. Pregnant or nursing women, and those of childbearing potential who were deemed unlikely to be using adequate contraceptive measures during the course of the study were excluded. The study was performed according to the ethical principles of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Uppsala, Sweden, prior to study commencement. Informed written consent was obtained from all participating patients.

Study Design. This was a single-center, randomized, open-label, crossover study comprising two five-day treatment periods separated by a washout interval of at least 13 days. An initial screening visit included determination of patients' complete medical history, physical examination, and measurement of laboratory safety variables as well as an assessment of *H. pylori* status using the [^{13}C] urea breath test.

Eligible patients were randomized to receive esomeprazole 40 mg or omeprazole 40 mg capsules once daily in the morning. Doses were administered 30 min before breakfast.

No antisecretory or prokinetic drugs were allowed for two weeks before and during each study period. Antacids were allowed as required for the control of reflux symptoms during the period up to midnight on the day preceding the clinic visit, but were not permitted on study days 1 or 5. Other concomitant medication considered necessary for the patients' welfare was administered at the investigator's discretion. Medication bottles were checked on day 5 of each treatment period to assess treatment compliance.

Alcohol was prohibited for two days before and during each treatment period and during the interval prior to the follow-up visit. Food and beverages, except water, were not permitted for 12 hr before the dose and 30 min after the dose on days 1 and 5 in each treatment period. Water was not permitted from midnight the previous evening until 30 min after the dose except for drug dosing. All meals were standarized during study days 1 and 5 to ensure consistent intragastric pH measurements were determined.

Measurement of Intragastric pH. After an overnight fast patients came to the clinic on days 1 and 5 of each dosing period. Study medication was administered under the supervision of study personnel, and 24-hr intragastric pH was recorded using a microelectrode (Ingold bipolar glass) linked to a Digitrapper pH 400 recorder (Medtronic Synetics AB). The electrode was positioned 10 cm below the lower esophageal sphincter. The percentages of time with intragastric pH $>$ 3 and pH $>$ 4 along with 24-hr median intragastric pH were calculated for each patient during each recording period using the Polygram 98 PH programe (Medtronic Synetics AB).

Safety and Tolerability. All spontaneously reported adverse events, as well as those elicited by open questioning or observed by the investigator, were recorded. Blood and urine sampling for screening of routine laboratory safety variables was performed at the prestudy visit, at the end of each treatment period, and at the follow-up visit. Patients with clinically significant changes in laboratory variables were either excluded or withdrawn from the study and/or followed-up until normalization or for as long as the investigator considered necessary.

Statistical Analysis. The study was designed to enroll a maximum of 130 patients and to have 115 evaluable patients, thereby providing an estimated power of 99% for a two-sided paired *t*test at the 5% significance level.

The percentage of time with intragastric pH $>$ 4 and pH $>$ 3 as well as 24-hr median pH during the 24-hr period following drug administration was analyzed using a mixed-model ANOVA with fixed effects for period, sequence, and treatment and a random effect for patient within sequence. The mean value for each treatment and the mean treatment difference (esomeprazole − omeprazole) were estimated with 95% confidence intervals (CIs). The percentage of time with intragastric pH $>$ 4 on day 5 was the primary outcome variable. The interpatient variability in percentages of time with intragastric pH $>$ 4 on day 1 and on day 5 was evaluated by testing for equal variance where the estimated variances are correlated, according to the method

Table 1. Baseline Demographics and Clinical Characteristics of Randomized Patients ($N = 130$)

Gender, male:female (%)	60:70 (46:54%)
Age [years, mean (range)]	31.7 (20–79)
Body weight, [kg, mean (range)]	74.4 (51–100)
Smokers, [*N* (%)]	32 (25%)
Duration of GERD symptoms [*N* (%)]	
<1 year	12 (9%)
1–5 years	66 (51%)
>5 years	52 (40%)

described by Snedecor and Cochran(16). Data for days 1 and 5 were analyzed separately. Adverse events are presented descriptively.

RESULTS

Patients. Baseline demographic and clinical characteristics of the 130 patients randomized to treatment are summarized in Table 1. All patients were Caucasian except for one who was black. Approximately 25% of patients were smokers. The specific reflux symptoms (epigastric pain, heartburn, regurgitation, and water brash) were of mild to moderate intensity in most patients.

Of the 130 randomized patients, a total of 120 completed the study; 10 patients discontinued due to either adverse events ($N = 5$) or other reasons ($N = 5$) and were excluded from the intragastric pH analysis. In addition, due to technical failure, pH recording data was missing for a further nine patients on day 1 ($N = 5$) and/or day 5 ($N = 5$), all of whom were excluded from the intragastric pH analysis for corresponding study days. A further patient who received the wrong study drug on day 5 of the first study period was also excluded from the pH analysis for day 5. All other patients completing the study took the study drugs according to the protocol. Therefore, 115 patients were analyzed for intragastric pH on day 1 and 114 on day 5.

Intragastric pH. The mean percentage of time with intragastric pH > 4 was significantly greater with esomeprazole 40 mg than with omeprazole 40 mg on day 1 (48.6% vs 40.6%, $P < 0.001$) and day 5 (68.4% vs 62.0%, $P < 0.001$) (Table 2). The estimated mean value for the difference between treatment groups was 8.1% and 6.4% on days 1 and 5, respectively, which corresponds to an additional 1.9 hr and 1.5 hr over the 24-hr period with intragastric pH > 4 following esomeprazole treatment on day 1 and day 5, respectively. Similarly, the percentage of time with intragastric pH > 3 was significantly higher with esomeprazole 40 mg than with omeprazole 40 mg on day 1 (63.3% vs 55.6%, $P < 0.001$) and day 5 (79.9% vs 74.9%, $P < 0.001$) (Table 2). Consequently, mean 24-hr median intragastric pH was significantly higher with esomeprazole 40 mg than with omeprazole 40 mg on both days 1 (3.86 vs 3.41, $P < 0.001$) and 5 (4.78 vs 4.50, $P < 0.001$) (Table 2).

Interpatient variability (as indicated by coefficient of variation) in the percentage of time with intragastric pH > 4 was significantly less with esomeprazole 40 mg (14.8%) than with omeprazole 40 mg (17.4%) on day 5 ($P = 0.02$ for test of equal variance).

In terms of individual patient responses, after five days of treatment an intragastric pH > 4 was maintained for at least 12 hr in 88% of patients receiving esomeprazole 40 mg and 75% of patients receiving omeprazole 40 g ($P < 0.01$). In addition, an intragastric pH > 4 was maintained for at least 16 hr in 55% and 44% of patients receiving esomeprazole 40 mg and omeprazole 40 mg, respectively ($P < 0.05$) (Figure 1).

Safety and Tolerability. Esomeprazole 40 mg daily was well tolerated, displaying a similar pattern and

Table 2. Pharmacodynamic Data Following Administration of Esomeprazole or Omeprazole Once Daily in Patients with Symptoms of Gastroesophageal Reflux Disease

	Treatment group					
	Day 1 (N = 115)			*Day 5 (N = 114)*		
	Esomeprazole 40 mg	*Omeprazole 40 mg*	*Esomeprazole − omeprazole*	*Esomeprazole 40 mg*	*Omeprazole 40 mg*	*Esomeprazole − omeprazole*
Mean percent time with intragastric pH > 4 (95% CI)	48.6 (45.1, 52.2)	40.6 (37.0, 44.1)	8.1* (5.5, 10.7)	68.4 (65.4, 71.4)	62.0 (59.0, 65.0)	6.4* (4.0, 8.8)
Mean percent time with intragastric pH > 3 (95% CI)	63.3 (59.7, 66.8)	55.6 (52.0, 59.1)	7.7* (5.1, 10.4)	79.9 (77.5, 82.3)	74.9 (72.5, 77.3)	5.0* (3.1, 6.9)
Mean 24-hr median intragastric pH (95% CI)	3.86 (3.67, 4.05)	3.41 (3.22, 3.60)	0.45* (0.31, 0.60)	4.78 (4.64, 4.92)	4.50 (4.36, 4.64)	0.28* (0.17, 0.39)

*$P < 0.001$.

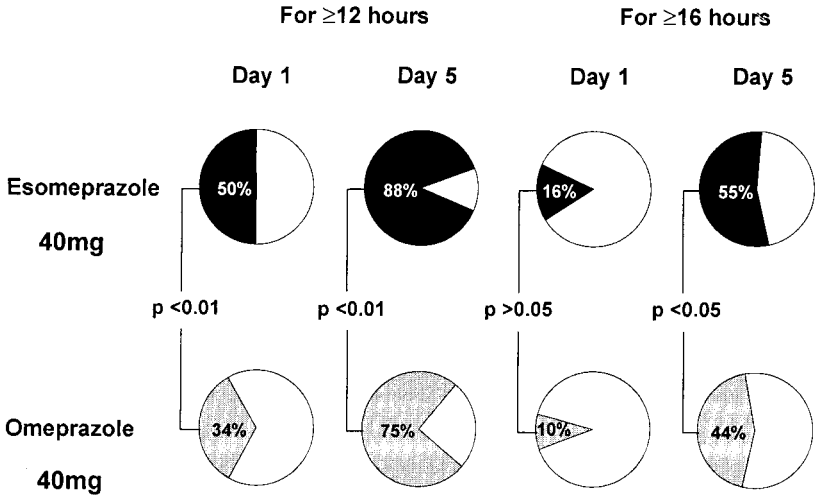

Fig 1. Percentage of patients maintaining intragastric pH > 4 for at least 12 and 16 hr of the 24-hr period, following treatment with esomeprazole 40 mg and omeprazole 40 mg once daily for five days.

incidence of adverse events to omeprazole 40 mg daily. The most commonly reported adverse events in either group were headache (~20%), nausea (~8%), and abdominal pain (~6%).

Abnormal laboratory values were reported in two patients at the last study visit; an increase in alkaline phosphatase after receiving omeprazole 40 mg during the second treatment period ($N = 1$) and an increase in alanine aminotransferase after receiving esomeprazole 40 mg during the second treatment period ($N = 1$). A decrease in platelet count also was observed at the last study visit in a third patient following treatment with esomeprazole 40 mg during the second treatment period. However, no particular trend was observed for changes in laboratory safety variables after esomeprazole or omeprazole treatment and no safety concerns were raised.

DISCUSSION

In GERD, the degree of mucosal injury (1) and frequency of reflux symptoms (17) are a function of esophageal acid exposure. Indeed, the response to antisecretory agents can be predicted by the duration of suppression of intragastric acidity (as indicated by a pH > 4) over the 24-hr period (1). Therefore, maintaining intragastric pH > 4 is important in achieving esophageal healing and symptom relief in GERD.

In the present study, intragastric pH > 4 was maintained for significantly longer with esomeprazole 40 mg than with omeprazole 40 mg after both single and repeated once-daily dose administration in patients with symptoms of GERD. These findings reinforce previous evidence regarding the greater acid-suppressant effect of esomeprazole 40 mg compared with omeprazole 20 mg in patients with symptoms of GERD (10). Importantly, doubling the omeprazole dose from the recommended standard dose of 20 mg to 40 mg does not deliver the same long-lasting degree of acid control that is provided by esomeprazole 40 mg. Indeed, intragastric pH remained above 4 for approximately 2 hr longer with esomeprazole 40 mg than omeprazole 40 mg when assessed on day 1, and 1.5 hr longer when assessed on day 5. Furthermore, when compared with omeprazole 40 mg, esomeprazole 40 mg was associated with significantly less interindividual variation in the percentage of time with intragastric pH > 4. Interestingly, marked intersubject variability in the degree of acid control obtained with omeprazole 40 mg daily has been reported in a previous study in healthy volunteers (8).

The improved intragastric pH control noted with esomeprazole 40 mg in the present study (as reflected in an intragastric pH > 4 for 68% of the 24-hr period) is in close agreement with previous findings with this PPI (intragastric pH > 4 for 70% of the 24-hr period) (10). Importantly, these pharmacodynamic findings also reinforce those of previous 24-hr intragastric pH studies, indicating greater acid control with esomeprazole 40 mg over standard doses of lansoprazole (11), pantoprazole (12), and rabeprazole (13).

Since a correlation has been suggested between

duration of acid exposure and severity of both esophagitis and GERD symptoms (17, 18), an improved acid control with esomeprazole should manifest in higher rates of symptom control and increased rates of esophageal healing. Indeed, this theory has recently been confirmed in two large clinical studies comparing esomeprazole 20 or 40 mg with omeprazole 20 mg (14, 15). The clinical relevance of the difference in acid control between esomeprazole 40 mg and omeprazole 40 mg observed in the present study has to be proven in larger clinical studies.

The effect on gastrin levels was not investigated in this short-term study, but a recently published 12-months long-term study in patients with healed erosive esophagitis showed that gastrin levels increased, as expected, and reached a plateau after three months of treatment with esomeprazole 40 mg od. No changes in gastric histology were noted in the majority of patients and no safety concerns arose (19).

The results of the present study indicate that once-daily esomeprazole 40 mg is well tolerated and demonstrates greater acid control and reduced interpatient variability when compared with double the standard 20 mg dose of omeprazole (ie, 40 mg once daily). Furthermore, the improved intragastric pH control offered by esomeprazole 40 mg provides a rationale for the use of this PPI in the treatment of GERD and other acid-related disorders.

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