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Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease

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SUMMARY

Background: Esomeprazole (Nexium) is a new proton pump inhibitor for the treatment of acid-related diseases.

Methods: In this double-blind crossover study, 38 patients with gastro-oesophageal reflux disease (GERD) symptoms were randomized to esomeprazole 40 and 20 mg and omeprazole 20 mg once daily for 5 days. On day 5 of each dosing period, 24-h intragastric pH and pharmacokinetic variables were measured.

Results: Thirty-six patients aged 29–58 (mean 45) years completed the study. Esomeprazole 40 and 20 mg maintained intragastric pH > 4 for (mean) 16.8 and 12.7 h, respectively, vs. 10.5 h for omeprazole 20 mg ($P < 0.001$ and $P < 0.01$). Twenty-four-hour median intragastric pH was significantly higher with esomeprazole 40 mg (4.9) and 20 mg (4.1) than with omeprazole 20 mg (3.6) ($P < 0.001$ and $P < 0.01$). Area under the plasma concentration–time curve (*AUC*) was 80% higher for esomeprazole 20 mg vs. omeprazole, while that for esomeprazole 40 mg was more than five times higher (each $P < 0.0001$). Interpatient variability in intragastric pH and *AUC* was less with esomeprazole than with omeprazole. Esomeprazole was well tolerated and there were no safety concerns.

Conclusions: Esomeprazole provides more effective acid control than omeprazole, with reduced interpatient variability, thereby offering the potential for improved efficacy in acid-related diseases.

INTRODUCTION

It is well established that the aggressiveness of the gastric refluxate (as reflected in the degree of mucosal injury), along with the associated symptoms of gastro-oesophageal reflux disease (GERD), are highly pH dependent. In this regard, an intragastric acidity threshold of pH 4 serves to differentiate between aggressive and nonaggressive reflux, because a refluxate of pH < 4 not only contains active pepsin but also leads to more intense symptoms.[1, 2] Strategies aimed at maintaining intragastric pH above this threshold represent the key to effective management of GERD, because mucosal healing correlates directly with the proportion of the 24-h period with intragastric pH > 4.[3] This relationship explains why the effective, sustained acid control provided by proton pump inhibitors leads to prompt resolution of symptoms and high rates of oesophageal healing.[4, 5] Proton pump inhibitors have therefore emerged as the initial treatment of choice for the management of GERD, as endorsed by the recent Genval Workshop Group.[6]

Omeprazole, like other proton pump inhibitors, is a substituted benzimidazole that exists as a racemic mixture of the *R*- and *S*-isomers. Esomeprazole (Nexium; Astra Zeneca R&D, Sweden) is the *S*-isomer

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of omeprazole and the first proton pump inhibitor to be developed as a single isomer for the treatment of acid-related diseases. In common with omeprazole, esomeprazole demonstrates highly effective inhibition of gastric acid secretion.[7] Esomeprazole differs from omeprazole, however, in displaying lower first-pass hepatic metabolism and slower plasma clearance, resulting in higher plasma concentrations.[8] The increased systemic bioavailability of esomeprazole offers the prospect of improved clinical efficacy and more effective management of acid-related diseases.

The aim of this study was to compare the acid inhibitory effects, pharmacokinetics and safety of esomeprazole and omeprazole in patients with GERD. Comparisons were performed between the recommended dosage of omeprazole (20 mg once daily) and the corresponding dosage of esomeprazole; in addition the effects of a higher esomeprazole dosage (40 mg once daily) were investigated for evidence of a dose–response relationship.

METHODS

Patients

Male and female patients with symptoms of suspected or confirmed (by investigation) GERD, aged 30–60 years, were eligible for inclusion. The main exclusion criteria were symptoms of gastrointestinal bleeding (e.g. melaena, haematemesis), any pharmacotherapy for GERD within the previous 2 weeks, and previous history of oesophago-gastric surgery. Patients with a history of alcoholism or drug abuse and those with significant concomitant diseases likely to interfere with the results of the study were also excluded from enrolment. Pregnant or nursing women, and those not likely 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 independent Ethics Committee of the University of Gothenburg, Sweden, prior to study commencement. Informed written consent was obtained from all patients.

Study design

The study used a double-blind, randomized, crossover design, comprising three 5-day dosing periods separated by washout intervals of at least 2 weeks. An initial screening visit comprised determination of patients' complete medical history, physical examination and measurement of laboratory safety variables, as well as a serological assessment of *Helicobacter pylori* status using routine methods. Eligible patients were randomized to receive oral therapy with esomeprazole 40 mg o.d., esomeprazole 20 mg o.d. or omeprazole 20 mg o.d. Doses were to be administered at least 30 min before breakfast. In order to maintain patient and investigator blinding, all study medication was identical in appearance and comprised enteric-coated pellets within gelatine capsules. During the washout periods, patients were allowed to use antacids as needed for relief of reflux symptoms. Concomitant treatment with H_2-receptor antagonists, prokinetic drugs or other proton pump inhibitors was not permitted during the study.

Measurement of intragastric pH

After an overnight fast, patients returned to the clinic on day 5 of each dosing period. Study medication was administered under the supervision of the investigator, after which 24-h intragastric pH was recorded using a microelectrode (Ingold bipolar glass; Mettler-Toledo GmbH, Switzerland) linked to a Digitrapper MK III recorder (Synectics AB, Sweden). The electrode was inserted transnasally and positioned about 10 cm below the lower oesophageal sphincter. Patients were mobile throughout the recording, and were instructed not to lie down for periods longer than 10 min during the day. Data were analysed using EsopHogram software (Synectics AB, Sweden) to calculate the percentage of the 24-h period for which intragastric pH exceeded 4, along with 24-h median intragastric pH. To ensure consistency of results, food and beverage intake was standardized throughout each day of intragastric pH measurement for all patients.

Pharmacokinetics

Venous blood samples were drawn at regular intervals up to 8 h after drug administration for pharmacokinetic determinations on day 5 of each dosing period. Plasma concentrations of esomeprazole and omeprazole were measured using normal-phase liquid chromatography and ultra-violet detection, as previously described.[9] The following pharmacokinetic variables were determined: area under the plasma concentration–time curve

(*AUC*); maximum plasma concentration (C_{max}); terminal half-life ($t_{½\lambda z}$); and time to C_{max} (t_{max}). *AUC* was determined using the log-linear trapezoidal method (the residual area after the last data point was calculated as $C_{last}/\lambda z$, where C_{last} is the concentration at the last measurable data point and λz the terminal slope of the plasma concentration–time profile). $t_{½\lambda z}$ was calculated as $\ln 2/\lambda z$, while t_{max} was determined from the plasma concentration–time profile.

Safety and tolerability

All adverse events spontaneously reported, as well as those elicited by open questioning or observed by the investigator, were recorded. Routine laboratory safety variables, including blood and urine analysis, were assessed before and at the end of the study (2–5 days after completion of the last dosing period). Clinically significant changes in laboratory variables were followed up for as long as medically necessary.

Statistical analysis

Differences between treatment groups in 24-h median intragastric pH, the duration for which intragastric pH was > 4 and *AUC* were analysed using a mixed-model analysis of variance, with fixed effects for period, carry-over and treatment and a random effect for patients. Estimated means and treatment differences, together with 95% confidence intervals, were calculated. *AUC* values were log-transformed before the analysis. The results for *AUC* were then calculated by taking the exponential of the estimates, and are presented as geometric means together with 95% confidence intervals.

RESULTS

A total of 36 of 38 enrolled patients completed the study. One discontinuation was due to nonattendance, and another patient withdrew from the study as a result of an adverse event (tiredness) during a washout interval. Baseline demographic and clinical characteristics of the patients completing the study are shown in Table 1. All patients were Caucasian, and the majority (83%) were *H. pylori*-negative. About one-third of patients were smokers.

Counting of returned study medication indicated 100% compliance during each active dosing period. No patient received concomitant medication during the study that was deemed likely to have affected the pharmacodynamic or pharmacokinetic findings.

Intragastric pH

The intragastric pH–time profiles following oral administration of esomeprazole and omeprazole are shown in Figure 1. For both dosages of esomeprazole the percent-

Table 1. Baseline demographics and clinical characteristics of evaluable patients (n = 36)

Gender, male : female (%)	42 : 58
Mean age, years (range)	45 (29–58)
Mean bodyweight, kg (range)	80 (46–108)
Positive *H. pylori* status (no. of patients)*	6 (17%)
Smokers (no. of patients)	13 (36%)
Duration of GERD (no. of patients)	
1–5 years	9
> 5 years	27

* As determined by serology.

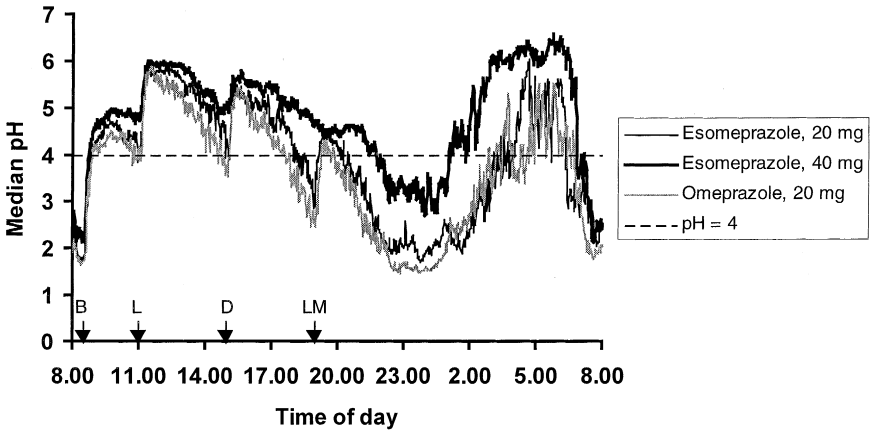

Figure 1. Twenty-four-hour median intragastric pH–time profiles after 5 days' dosing with esomeprazole (40 and 20 mg once daily) and omeprazole (20 mg once daily) in 36 patients with symptoms of gastro-oesophageal reflux disease; arrows indicate timepoints at which standardized meals were served.

Table 2. Effect of 5 days' dosing with esomeprazole or omeprazole on intragastric acidity in 36 patients with symptoms of gastro-oesophageal reflux disease

Variable	Treatment group*		
	Esomeprazole 40 mg	Esomeprazole 20 mg	Omeprazole 20 mg
Mean duration (hours) with intragastric pH > 4 (95% CI)	16.8 (15.0–18.4)‡	12.7 (11.0–14.4)†	10.5 (8.8–12.2)
Mean percentage of 24-h period with intragastric pH > 4 (95% CI)	69.8 (62.3–76.8)‡	53.0 (46.0–60.0)†	43.7 (36.7–50.7)
24-h median intragastric pH (95% CI)	4.9 (4.5–5.2)‡	4.1 (3.8–4.5)†	3.6 (3.2–3.9)

*All doses given once daily.
CI, confidence interval; †$P < 0.01$ vs. omeprazole; ‡$P < 0.001$ vs. omeprazole and esomeprazole 20 mg.

age of the 24-h period for which intragastric pH remained > 4 was significantly higher compared with omeprazole (Table 2). Thus, esomeprazole 40 mg maintained intragastric pH > 4 for about 6 h longer than omeprazole 20 mg (16.8 h vs. 10.5 h). This difference was about 2 h for esomeprazole 20 mg vs. omeprazole 20 mg (12.7 vs. 10.5 h, respectively). As a result, mean 24-h median intragastric pH was significantly higher for each dosage of esomeprazole compared with omeprazole. Furthermore, esomeprazole 40 mg was significantly more effective than the 20 mg dosage in terms of the pharmacodynamic response. The esomeprazole 40 mg dosage also produced less interpatient variability (as expressed by standard deviation) in the percentage of time for which intragastric acidity exceeded pH 4 (17.8%), compared with values of 19.7% and 22.8%, respectively, for esomeprazole 20 mg and omeprazole 20 mg.

In terms of individual patient responses, an intragastric pH > 4 was maintained for more than 12 h in 92%, 54% and 44% of patients receiving esomeprazole 40 mg, esomeprazole 20 mg and omeprazole 20 mg, respectively, and an intragastric pH > 4 was maintained for more than 16 h in 56%, 24% and 14% of patients, respectively (Figure 2).

A total of six patients were *H. pylori*-positive. In this patient sub-group there was no clinically relevant difference between the pharmacodynamic response to esomeprazole and omeprazole (data not shown).

Pharmacokinetics

Pharmacokinetic variables after 5 days' dosing with esomeprazole or omeprazole are summarized in Table 3. *AUC* following dosing with esomeprazole 20 mg was approximately 80% higher than with omeprazole 20 mg;

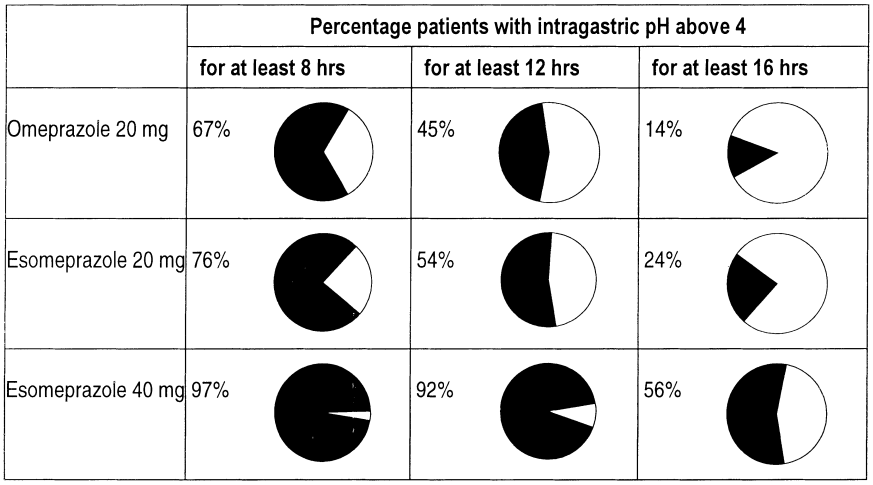

Figure 2. Percentage of patients maintaining intragastric pH > 4 for at least 8, 12 and 16 h after 5 days' dosing with esomeprazole (40 and 20 mg once daily) and omeprazole (20 mg once daily).

Table 3. Pharmacokinetic variables after 5 days' dosing with esomeprazole or omeprazole in 36 patients with symptoms of gastro-oesophageal reflux disease

Variable	Treatment group*		
	Esomeprazole 40 mg	Esomeprazole 20 mg	Omeprazole 20 mg
Geometric mean *AUC*, μmol · h/L (95% CI)	12.64 (9.89–16.17)	4.18 (3.27–5.35)	2.34 (1.83–3.00)
Median C_{max}, μmol/L (range)	5.13 (1.59–9.61)	2.42 (0.51–4.78)	1.41 (0.15–3.51)
Median $t_{½\lambda z}$, h (range)	1.6 (0.8–2.9)	1.3 (0.5–2.5)	1.0 (0.3–2.8)
Median t_{max}, h (range)	1.2 (1.0–4.0)	1.0 (0.5–8.0)	1.0 (0.5–6.0)

* All doses given once daily.
AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max}, maximum plasma concentration; $t_{½\lambda z}$, terminal half-life; t_{max}, time to C_{max}.

for esomeprazole 40 mg, *AUC* was over five times higher vs. omeprazole. These differences were statistically significant (each $P < 0.0001$). Interpatient variability (standard deviation, based on log-transformed values) in *AUC* was less with esomeprazole 40 mg (0.47) and 20 mg (0.64) than with omeprazole (0.73).

Mean plasma concentration–time profiles for esomeprazole 40 and 20 mg and omeprazole are shown in Figure 3. Overall, C_{max} values for each dosage of esomeprazole were higher than those observed for omeprazole (Figure 3 and Table 3), although t_{max} values were similar (median ~1 h) for all treatments. Plasma $t_{½\lambda z}$ values tended to be somewhat longer for esomeprazole (median 1.3 and 1.6 h) than for omeprazole (median 1.0 h) (Table 3).

Safety and tolerability

Both dosages of esomeprazole were well tolerated, and the profile and incidence of adverse events were similar to that observed with omeprazole 20 mg. The most commonly reported adverse events were gastrointestinal complaints (e.g. abdominal pain, nausea, diarrhoea), respiratory infection and headache. Such adverse events were typically mild and did not necessitate drug discontinuation. No serious adverse events occurred during, or as a result of, treatment and there were no clinically relevant changes in laboratory safety variables.

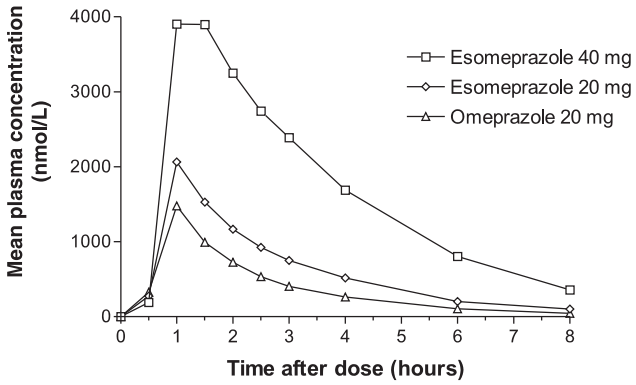

Figure 3. Mean plasma concentration–time profiles after 5 days' dosing with esomeprazole (40 and 20 mg once daily) and omeprazole (20 mg once daily) in 36 patients with symptoms of gastro-oesophageal reflux disease.

DISCUSSION

Frequent and prolonged oesophageal exposure to gastric refluxate is pivotal to the pathogenesis of GERD. Indeed, the degree of mucosal injury,[3] the frequency of reflux symptoms[10] and the severity of oesophageal pain[2] in GERD are functions of oesophageal acid exposure (i.e. duration of exposure and pH of the refluxate). Among the various intragrastric acidity thresholds that have been proposed to differentiate between aggressive and nonaggressive reflux, pH 4 appears optimal.[1] Consequently, maintenance of an intragastric pH above 4 for the greater part of each 24-h period is crucial for ensuring oesophageal healing and symptom relief in GERD.

Using this intragastric pH threshold, our findings show that esomeprazole achieves significantly greater acid control than omeprazole. Thus, esomeprazole increased the duration for which intragastric pH exceeded 4 and achieved a higher median intragastric pH across the entire 24-h period. These benefits were found with each dosage of esomeprazole (40 and 20 mg), although they were more pronounced with the 40 mg dosage. Indeed, the pharmacodynamic effect of esomeprazole 40 mg was significantly greater than that observed for the lower dosage. In view of this it would be pertinent to

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