Aliment Pharmacol Ther 2001; 15: 1563–1569.

Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole

T. ANDERSSON*, K. RÖHSS†, E. BREDBERG† & M. HASSAN-ALIN†
**Clinical Pharmacology, AstraZeneca LP, Wayne, PA, USA; and †Clinical Research & Development, AstraZeneca AB, Mölndal, Sweden*

Accepted for publication 6 June 2001

SUMMARY

Background: Esomeprazole, the S-isomer of omeprazole, is the first proton pump inhibitor developed as a single isomer for the treatment of acid-related diseases.
Aim: To examine the pharmacokinetics and pharmacodynamics of esomeprazole.
Methods: In a crossover study, 12 healthy males received 5, 10 or 20 mg of esomeprazole, or 20 mg of omeprazole, once daily over 5 days. The pharmacokinetics and effects on pentagastrin-stimulated peak acid output of esomeprazole and omeprazole were studied on days 1 and 5.
Results: The area under the curve (*AUC*) of both esomeprazole and omeprazole increased from day 1 to day 5. The correlation between acid inhibition and *AUC* for esomeprazole could be well described with a sigmoid E_{max} model. The mean inhibition values of the pentagastrin-stimulated peak acid output on day 1 for 5, 10 and 20 mg of esomeprazole were 15%, 29% and 46%, respectively; the corresponding day 5 values were 28%, 62% and 90%. The mean inhibition values of the pentagastrin-stimulated peak acid output for omeprazole were 35% (day 1) to 79% (day 5).
Conclusions: The pharmacokinetics of esomeprazole are time and dose dependent. There was a good correlation between *AUC* and effect for esomeprazole. These data suggest an increased acid inhibitory effect of esomeprazole compared to omeprazole.

INTRODUCTION

Omeprazole, the first proton pump (H^+, K^+-ATPase) inhibitor, has been used for over a decade in the treatment of acid-related diseases. Like subsequent proton pump inhibitors, omeprazole is metabolized primarily by a polymorphically expressed enzyme within cytochrome P450 (CYP), CYP2C19.[1] Omeprazole is a racemic composition of its two optical isomers, S-omeprazole (esomeprazole) and R-omeprazole, which have demonstrated stereoselective metabolisms.[2–4] Esomeprazole is metabolized to a lesser degree than R-omeprazole by CYP2C19. Esomeprazole has also been shown to be metabolized at a lower rate, resulting in higher plasma levels,[4] which, because the area under the curve (*AUC*) directly correlates to the antisecretory effect,[5] promotes more effective acid control. Thus, esomeprazole's inhibitory effect on gastric acid secretion is greater than that of both omeprazole and its R-isomer. We investigated the relations between dose/concentration and response for esomeprazole and omeprazole after single and repeated doses.

Correspondence to: Dr T. Andersson, Clinical Pharmacology, AstraZeneca LP, 725 Chesterbrook Blvd., Wayne, PA 19087-5677, USA.
E-mail: tommy.andersson@astrazeneca.com

MATERIALS AND METHODS

Subjects

Twelve healthy males, mean age 24 years (range, 20–30 years) and mean weight 75 kg (range,

69–84 kg), completed this study. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the University of Göteborg's Medical Faculty Ethics Committee and by the Swedish Medical Products Agency. Each volunteer completed an informed consent document. Inclusion criteria were: (i) negative *Helicobacter pylori* status (assessed by urea breath test);[6] and (ii) normal response to pentagastrin [pentagastrin-stimulated peak acid output (PAO) ≥ 25 mmol/h at 90 μg/h infusion rate]. Four treatment periods, each lasting 5 days, were separated by 2-week washout periods. Within each treatment interval, subjects received either 5, 10 or 20 mg of esomeprazole, or 20 mg of omeprazole, once daily.

Materials

Esomeprazole was administered as the sodium salt in solution and omeprazole as enteric-coated granules in gelatin capsule form. The reason for not using a solid oral formulation of esomeprazole in this study is that it was not available at the time. However, in later studies, the bioavailability of an esomeprazole capsule relative to that of the solution has been shown to be complete, both at single and repeated dosing (AstraZeneca, data on file). The frozen stock solution of esomeprazole (5 mg/mL distilled water) was thawed immediately before administration and diluted with distilled water to a volume of 50 mL. To avoid degradation of the acid-labile compounds, a sodium bicarbonate buffer solution was given (0.16 mmol/mL; 100 mL with dose, 50 mL 5 min before and at 10, 20 and 30 min after) to neutralize gastric acid. Subjects swallowed omeprazole capsules with water.

Methods

Alcohol and all medications, including over-the-counter drugs, were prohibited for the 2 days before and throughout the 5 days of the four treatment periods. Subjects fasted from 22:00 hours on the nights preceding investigational days 1 and 5 and reported to the laboratory at 08:00 hours the following morning. An indwelling cannula for blood sampling was inserted and secured in a forearm vein. Blood samples were drawn 5 min before (reference sample) and at 15, 30 and 45 min, and 1, 2, 3, 4 and 6 h after the dose. Blood was kept at room temperature in heparinized tubes for at least 5 min, and then centrifuged for 10 min. The plasma was transferred to plastic tubes and kept frozen (–20 °C); it was then analysed for parent compounds and the hydroxy and sulphone metabolites, using liquid chromatography with UV detection.[7]

Subjects had gastric secretion tests once before the ingestion of the study drugs and beginning 6 h after dosing on days 1 and 5. If a subject's first test indicated a normal response to pentagastrin, this result was used as baseline. An indwelling cannula for pentagastrin infusion was inserted in a forearm vein (other than the one used for blood sampling). A double-lumen nasogastric tube with an attached polyethylene catheter was introduced through the nasal passage. The stomach was continuously perfused through the catheter with an inert marker solution, and the contents were continuously aspirated. After the collection of basal secretion, pentagastrin (90 μg/h) was administered intravenously, and gastric acid was collected for four consecutive 15-min periods.

Data analysis and statistical evaluation

The pharmacokinetic parameters for esomeprazole and omeprazole were calculated using non-compartmental methods. The maximum response to pentagastrin stimulation was measured as PAO, calculated as the sum of the two highest consecutive 15-min samples multiplied by two and expressed as mmol/h. The percentage change in PAO after drug intake, relative to the control acid secretion test before drug intake, was calculated.

The pharmacodynamic and pharmacokinetic data for the 12 subjects were analysed with a mixed-model analysis of variance (ANOVA), designating period and treatment as fixed effects and subject as a random effect. Pharmacokinetic variables were log-transformed before analysis, but pharmacodynamic data were original. Estimates and 95% confidence limits of log-transformed variables were anti-logarithmized, and the results were presented as geometric means and the ratio thereof, with confidence intervals.

The relation between esomeprazole concentrations (in terms of either *AUC* or C_{max}) and the effect on acid inhibition was described by means of the following E_{max} models:

$$\text{Acid inhibition} = (E_{max} \times AUC^s)/(AUC_{50}^s + AUC^s)$$

and

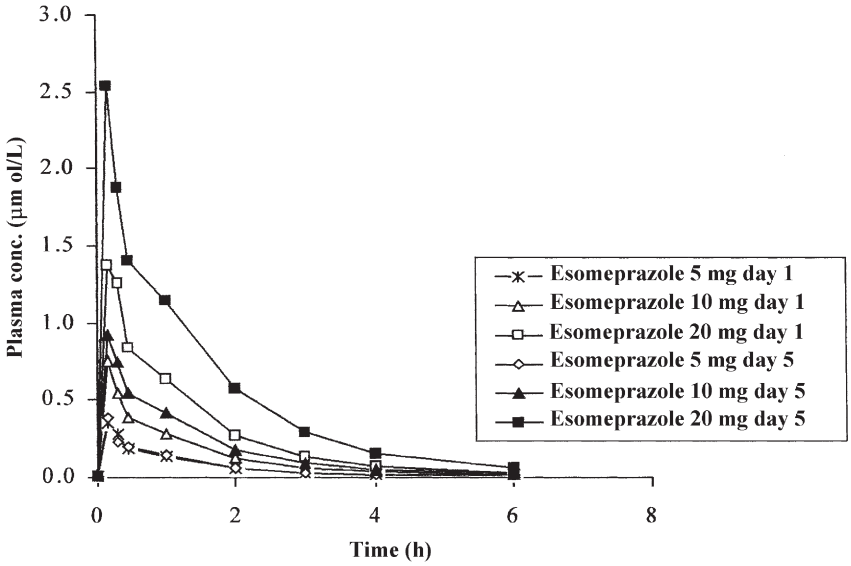

Figure 1. Mean plasma concentrations of esomeprazole, 5, 10 and 20 mg, on days 1 and 5 in 12 healthy males.

$$\text{Acid inhibition} = (E_{max} \times C^s_{max})/(C^s_{max50} + C^s_{max})$$

where E_{max} is the maximum inhibitory effect and AUC_{50} and C_{max50} are the AUC and C_{max} values, respectively, at which 50% inhibition occurs. The s is the slope or sigmoidicity factor.

The data from days 1 and 5 were analysed separately. The computer software used for the pharmacokinetic and pharmacodynamic analysis was WinNonlin Pro, version 1.5 (Scientific Consulting Inc.). The data from the omeprazole treatment were too scarce to be analysed with any precision as only one dose of omeprazole was given.

RESULTS

Figure 1 depicts the mean plasma levels on days 1 and 5 for the three doses of esomeprazole. Table 1 presents

Table 1. Geometric mean (95% confidence interval) pharmacokinetic parameter values on days 1 and 5 of oral dosing with different doses of esomeprazole (solution) or omeprazole (capsule) to 12 healthy males (from Andersson *et al.*[13] with permission)

	Esomeprazole			Omeprazole
	5 mg	10 mg	20 mg	20 mg
Day 1				
C_{max} (μmol/L)	0.35 (0.27–0.47)	0.79 (0.59–1.05)	1.68 (1.26–2.23)	0.62 (0.47–0.83)
t_{max} (h)*	0.31 (0.24–0.38)	0.30 (0.24–0.36)	0.38 (0.29–0.46)	1.94 (1.35–2.53)
AUC (μmol·h/L)	0.29 (0.19–0.45)	0.65 (0.42–1.01)	1.47 (0.95–2.28)	1.25 (0.81–1.94)
$t_{1/2}$ (h)	0.50 (0.36–0.71)	0.68 (0.53–0.86)	0.74 (0.58–0.95)	0.98 (0.70–1.35)
Day 5				
C_{max} (μmol/L)	0.42 (0.33–0.54)	0.98 (0.77–1.25)	2.55 (2.00–3.24)	1.00 (0.79–1.27)
t_{max} (h)*	0.31 (0.21–0.41)	0.33 (0.25–0.41)	0.29 (0.23–0.35)	1.23 (0.93–1.53)
AUC (μmol·h/L)	0.33 (0.22–0.49)	0.98 (0.66–1.46)	3.10 (2.09–4.61)	1.86 (1.25–2.77)
$t_{1/2}$ (h)	0.59 (0.42–0.82)	0.80 (0.62–1.03)	1.10 (0.88–1.38)	1.09 (0.78–1.52)
Day 5/day 1				
C_{max}	1.19 (0.97–1.46)	1.25 (1.02–1.53)	1.52 (1.24–1.86)	1.60 (1.31–1.96)
t_{max} (h)†	0.00 (−0.14–0.14)	0.04 (−0.07–0.16)	−0.08 (−0.16–(−0.01))	−0.71 (−1.14–(−0.28))
AUC	1.14 (0.97–1.35)	1.51 (1.27–1.78)	2.11 (1.78–2.49)	1.49 (1.26–1.76)
$t_{1/2}$	1.17 (1.04–1.32)	1.18 (1.07–1.30)	1.49 (1.28–1.74)	1.12 (0.80–1.57)

*Arithmetic mean.
†Difference between day 5 and day 1.

Table 2. Geometric mean of AUC_{0-t} (μmol·h/L) for hydroxy and sulphone metabolites and 95% confidence intervals for the ratios of the true treatment effects between day 1 and day 5 and for each day separately

	Esomeprazole			Omeprazole
	5 mg	10 mg	20 mg	20 mg
Hydroxy metabolite				
Day 1	0.018 (0.013–0.027)	0.076 (0.055–0.105)	0.24 (0.17–0.33)	1.13 (0.82–1.56)
Day 5	0.022 (0.015–0.032)	0.084 (0.060–0.120)	0.33 (0.24–0.47)	1.38 (0.99–1.93)
Day 5/day 1	1.28 (0.90–1.84)	1.11 (0.81–1.50)	1.42 (1.04–1.93)	1.22 (0.90–1.66)
Sulphone metabolite				
Day 1	0.14 (0.08–0.25)	0.43 (0.25–0.75)	1.08 (0.62–1.87)	0.44 (0.26–0.77)
Day 5	0.20 (0.12–0.32)	0.69 (0.42–1.12)	2.41 (1.48–3.93)	0.85 (0.52–1.38)
Day 5/day 1	1.36 (1.15–1.62)	1.59 (1.34–1.89)	2.23 (1.88–2.65)	1.91 (1.61–2.26)

the corresponding pharmacokinetic parameters. The AUC_{0-t} values for the metabolites are presented in Table 2.

On day 1, esomeprazole plasma levels showed a dose-proportional increase, and the *AUC* of esomeprazole, 20 mg, was slightly higher than that of omeprazole, 20 mg. For both compounds, the *AUC* was higher on day 5 than on day 1, and relations between dose and *AUC* were non-linear on day 5. Over the 5 days, the *AUC* values for the 5, 10 and 20 mg doses of esomeprazole increased by 14%, 51% and 111%, respectively, and by 49% for omeprazole, 20 mg. The steady-state *AUC* of esomeprazole at repeated dosing was 67% higher than that of omeprazole after 20 mg doses of each compound.

The concentration of the sulphone metabolite was higher on day 5 compared to day 1, both after esomeprazole and omeprazole. This increase was amplified at higher doses and most pronounced with esomeprazole, 20 mg. The concentration of the hydroxy metabolite was substantially higher during 20 mg omeprazole treatment compared to treatment with 20 mg esomeprazole, whereas the sulphone metabolite levels were lower with omeprazole.

The inhibitory effect of esomeprazole on pentagastrin-stimulated PAO was dose dependent (Tables 3 and 4, Figure 2) and more pronounced on day 5 compared with day 1 (Tables 3 and 4). The average pre-treatment PAO was 34 mmol/h for this group of healthy subjects (Table 3). On day 1, the mean inhibition of PAO was 15%, 29% and 46% for 5, 10 and 20 mg of esomeprazole, respectively; corresponding day 5 values were

Table 3. Mean (95% confidence interval) peak acid output (PAO) in mmol/h during pentagastrin stimulation at baseline prior to administration of drug and on days 1 and 5 of oral dosing with different doses of esomeprazole (solution) and omeprazole (capsule) in 12 healthy males

	Study day	PAO (mmol/h)
Baseline		34.5 (30.2–38.8)
Esomeprazole, 5 mg	1	29.2 (24.4–34.1)
	5	24.5 (18.4–30.5)
Esomeprazole, 10 mg	1	24.1 (18.4–29.9)
	5	12.0 (7.6–16.4)
Esomeprazole, 20 mg	1	18.8 (12.1–25.5)
	5	3.7 (1.1–6.2)
Omeprazole, 20 mg	1	21.9 (15.8–28.0)
	5	7.1 (2.3–11.8)

Table 4. Mean percentage inhibition (95% confidence interval) of pentagastrin-stimulated gastric acid secretion during administration of esomeprazole in doses of 5, 10 or 20 mg, or omeprazole, 20 mg, in 12 healthy males

	Esomeprazole			Omeprazole
	5 mg	10 mg	20 mg	20 mg
Day 1	14.6 (1.8–27.4)	29.2 (16.4–42.0)	45.7 (32.9–58.5)	35.4 (22.6–48.2)
Day 5	27.8 (16.2–39.4)	62.1 (50.5–73.7)	89.8 (78.2–101.4)	78.7 (67.1–90.3)
Day 5 – day 1	13.2 (2.1–24.3)	32.9 (21.7–44.0)	44.1 (33.0–55.2)	43.3 (32.2–54.4)

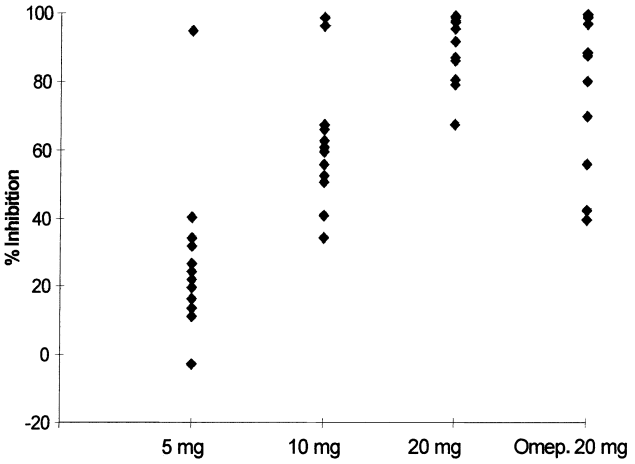

Figure 2. Dose vs. response (percentage inhibition of pentagastrin-stimulated gastric acid secretion) relations for 5, 10 and 20 mg doses of esomeprazole compared with omeprazole, 20 mg, on day 5 in 12 healthy males.

28%, 62% and 90%. The mean inhibition of PAO for omeprazole, 20 mg, rose over the 5-day period from 35% to 79%. The PAO effect and *AUC* correlated significantly on both investigational days (Figure 3). The observed data on acid inhibition and *AUC* of esomeprazole were better described with the E_{max} model than were data on acid inhibition and C_{max}, as shown in Figure 3; this was demonstrated by the lower standard errors (s.e.) for the parameters describing this relationship and presented in Table 5. The *AUC* needed to achieve an antisecretory effect of 80% was lower on day 5 (an *AUC* of only 2 μmol·h/L) than on day 1 (an *AUC* of approximately 4 μmol·h/L).

Daily doses of esomeprazole up to 20 mg for 5 days were well tolerated. Adverse effects were those commonly reported in volunteer studies and were all mild or moderate. Adverse effect patterns were similar for all

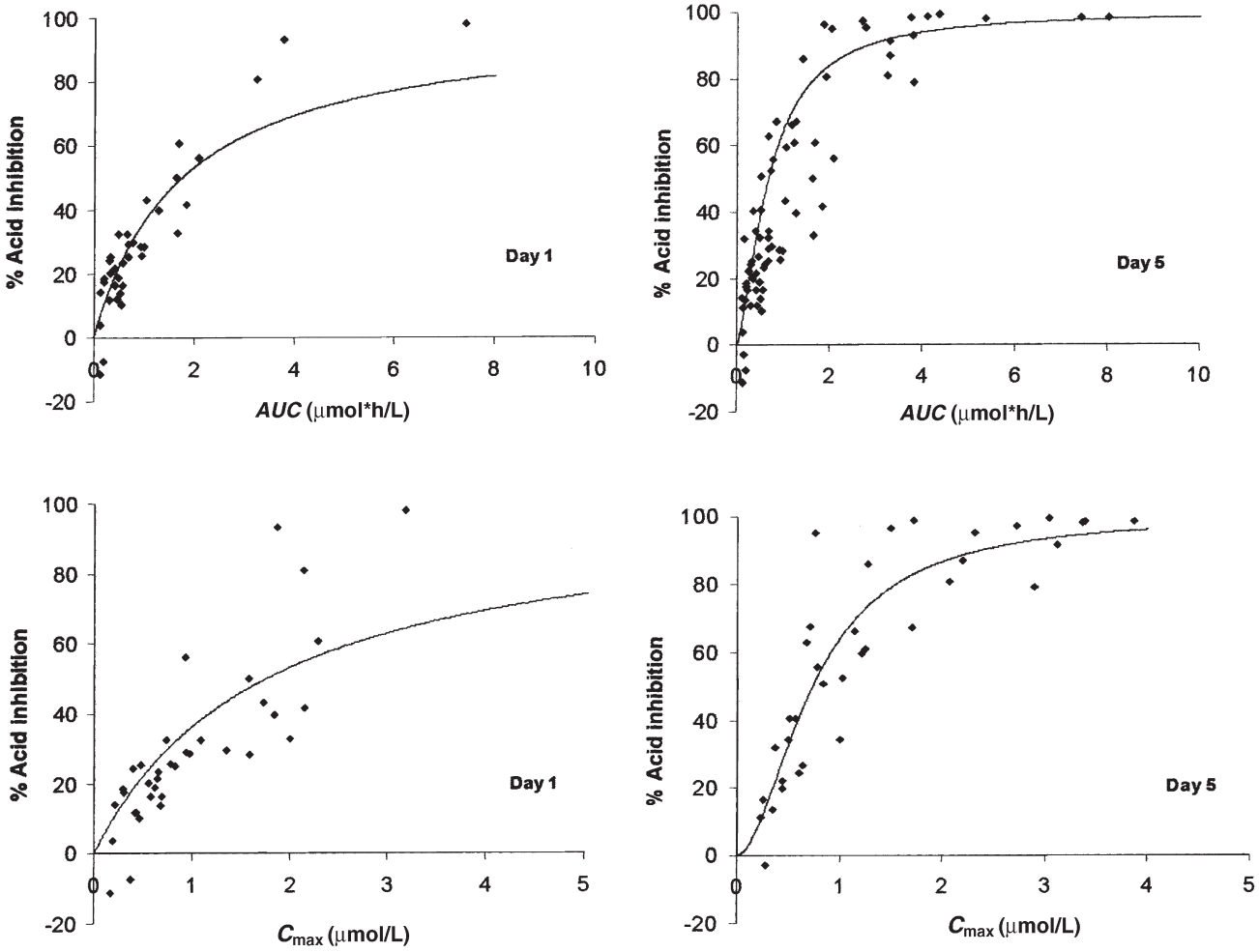

Figure 3. Percentage acid inhibition vs. *AUC* (upper panel) and C_{max} (lower panel) of esomeprazole on day 1 (left) and day 5 (right). The lines represent the predicted acid inhibition according to the parameters in Table 4.

Table 5. Parameter estimates of a sigmoid E_{max} model fitted to gastric acid inhibition and *AUC* or C_{max} after single and repeated administration of 5, 10 and 20 mg esomeprazole to 12 healthy male subjects

Day	Parameter	Estimate	s.e.	CV
AUC				
1	E_{max}	100	17.0	17
1	AUC_{50}	1.6	0.5	32
1	*s*	1.3	0.2	19
5	E_{max}	100	5.6	6
5	AUC_{50}	0.7	0.1	11
5	*s*	1.5	0.2	15
C_{max}				
1	E_{max}	100	57.6	56
1	C_{max50}	1.6	1.4	85
1	*s*	1.5	0.6	41
5	E_{max}	100	8.9	9
5	C_{max50}	0.7	0.1	14
5	*s*	1.9	0.4	23

E_{max} = % inhibition; AUC_{50} = μmol·h/L; C_{max50} = μmol/L.

doses of esomeprazole and for omeprazole, 20 mg. Headache was the most frequently reported effect.

DISCUSSION AND CONCLUSIONS

Omeprazole has earlier been shown to have a time-dependent pharmacokinetic behaviour, with an increase in *AUC* over the first 5 days of administration.[8] This increase has been shown to be dose dependent.[8] This has also been shown with the S-isomer, esomeprazole.[9] The reason for this increase in *AUC* has been demonstrated to be a combination of a decreased systemic elimination and an increased bioavailability due to the decreased first pass metabolism. This study also shows that the increase in *AUC* of esomeprazole, 20 mg, is even higher than that of omeprazole, 20 mg (111% and 49%, respectively). In this study, esomeprazole was given as a solution, while omeprazole was given as a capsule. However, as the bioavailability of an esomeprazole capsule relative to that of the solution is complete both at single and repeated dosing (AstraZeneca, data on file), we expect similar findings after the administration of both compounds in capsule form. The difference in the pharmacokinetics of esomeprazole compared to omeprazole is due to the difference in hepatic metabolism. Äbelö *et al.* have shown that esomeprazole (the S-enantiomer) is metabolized to a relatively greater extent via CYP3A4 compared to the other optical isomer (R-omeprazole), which is almost completely metabolized via CYP2C19.[2] This explains some of the findings in the present study. Firstly, the plasma levels of the hydroxy metabolite, which is formed through CYP2C19, are higher following the administration of 20 mg of omeprazole than of 20 mg of esomeprazole. Secondly, the plasma levels of the sulphone metabolite, which is formed through CYP3A4, are higher after esomeprazole administration than after omeprazole administration.

There was a clear *AUC*–effect relationship for esomeprazole, in that *AUC* and the inhibitory effect on stimulated gastric acid secretion of esomeprazole were correlated. This could be adequately described using a sigmoid E_{max} model. The acid inhibitory effect was pronounced, both with esomeprazole and omeprazole, and increased with repeated dosing. The inhibitory effect on PAO was higher for esomeprazole, 20 mg, given in a solution (90%) than for omeprazole, 20 mg, given as a capsule (79%), as a higher *AUC* was obtained with esomeprazole. These results correspond with those of a recent study that described an almost two-fold difference in *AUC* between esomeprazole and omeprazole after repeated 15 mg doses,[4] and, accordingly, a more pronounced inhibitory effect on the PAO of esomeprazole was demonstrated (91% vs. 64%).

Omeprazole's antisecretory effect has been reported to be correlated to the *AUC* and not dependent on the plasma level at any given time.[10] Omeprazole in itself is inactive and not until it reaches the acidic compartment of the gastric parietal cell and transforms into the active inhibitor, the sulphenamide, can it bind to the H^+, K^+-ATPase and exert its highly selective acid inhibitory effect.[11] This study not only confirms the *AUC*–antisecretory effect correlation (a phenomenon evaluated extensively in another publication),[5] but it also shows how this correlation differs over time, requiring a lower *AUC* for maximum acid inhibition on day 5 than on day 1. Ours and similar findings[12] suggest that the increasing antisecretory effect seen with repeated dosing may result from factors other than increased *AUC*, for example, the mechanism of action of the proton pump inhibitor. Prolonged duration of the sulphenamide binding to the proton pumps can produce a cumulative effect in the early treatment phase as some proton pumps are already inhibited as the next dose is administered.

In conclusion, the pharmacokinetics of esomeprazole were time and dose dependent. The day 5 *AUC* was higher for esomeprazole than omeprazole at the same

dose. There was a good correlation between *AUC* and effect for esomeprazole. These data suggest an increased acid inhibitory effect of esomeprazole compared to omeprazole.

ACKNOWLEDGEMENT

This study was supported by a grant from AstraZeneca.

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