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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects

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Abstract *Objective*: To study the pharmacokinetics of esomeprazole, one of the optical isomers of omeprazole, after 20 mg or 40 mg single and repeated oral and intravenous administration to healthy subjects. The main metabolites of esomeprazole were also assessed after the 40-mg oral dose.
Methods: In two separate studies, 16 healthy male subjects and 16 healthy male and female subjects received intravenous doses of 20 mg and 40 mg esomeprazole, respectively, on the first investigation day. After a washout period of 5–14 days, the same doses (20 mg as a solution and 40 mg as a capsule) were given orally for 5 days and then again intravenously on day 6. Blood samples for determination of esomeprazole and its metabolites were collected 12 h or 24 h post-dose and were analysed using normal-phase liquid chromatography with ultraviolet (UV) detection. Pharmacokinetic parameters of esomeprazole and its metabolites were estimated using non-compartmental analysis. Geometric means and ratios of the geometric means together with 95% confidence intervals (CI) of the pharmacokinetic parameters were calculated using analysis of variance (ANOVA).
Results: Plasma clearance (CL) of esomeprazole decreased from 22 l/h to 16 l/h and from 17 l/h to 9 l/h following repeated dosing of 20 mg and 40 mg, respectively. Total area under the plasma concentration-time curve (AUC) increased (from 1.34 μmol × h/l to 2.55 μmol × h/l) with absolute bioavailability (F) being 50% on day 1 and 68% on day 5 after the 20-mg oral dose. AUC increased (from 4.32 μmol × h/l to 11.21 μmol × h/l) with F being 64% on day 1 and 89% on day 5 after the 40-mg oral dose. The plasma levels for esomeprazole sulphone were substantially higher on day 5 than on day 1, while those for 5-hydroxy esomeprazole were marginally higher on day 5 than on day 1 following repeated oral dosing of 40 mg esomeprazole. No side effects attributable to esomeprazole were noticed.
Conclusion: The increased AUC of esomeprazole with repeated dosing is probably due to a combination of a decreased first-pass elimination and a decreased systemic clearance.

Key words Esomeprazole · Pharmacokinetics · Single dose · Steady state

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Introduction

Esomeprazole is the first proton pump inhibitor (PPI) developed as an optical isomer (*S*-omeprazole) for the treatment of acid-related diseases. Like other PPIs [1], the metabolism of esomeprazole is mediated by the cytochrome P_{450} (CYP) isoforms CYP3A4 and CYP2C19, which form two main metabolites, esomeprazole sulphone and 5-hydroxy esomeprazole, respectively [2], both pharmacologically inactive. Esomeprazole is a potent inhibitor of gastric acid secretion. The compound accumulates in the acidic compartment of the parietal cells where the molecule is transformed to its active form, the suphenamide.

One recent study in which each of the optical isomers of omeprazole, esomeprazole and *R*-omeprazole was incubated with human liver microsomes [2] indicated a relatively higher dependence on CYP2C19 for the metabolism of *R*-omeprazole than esomeprazole. The data from human liver microsomal experiments also showed that the intrinsic clearance for esomeprazole was substantially

lower than that for *R*-omeprazole and, consequently, lower than that for the racemate [2]. In an in vivo study in healthy subjects [3], the plasma levels of esomeprazole were higher than those of omeprazole, while those of *R*-omeprazole were lower. The mean AUC (area under the plasma concentration–time curve) of esomeprazole on day 7 was almost twofold higher for esomeprazole than that for omeprazole, whereas the mean AUC of *R*-omeprazole was approximately 50% of that for omeprazole. Furthermore, an almost twofold higher AUC with resulting higher intra-gastric pH for esomeprazole than for omeprazole was shown in patients with symptomatic gastroesophageal reflux disease (GERD) [4]. The intrinsic clearance being lower for esomeprazole than for *R*-omeprazole and the racemate resulting in a twofold higher AUC may therefore provide better clinical effect in the treatment of acid related diseases.

The objective of the present investigation was to study the pharmacokinetics of esomeprazole after oral and intravenous (i.v.) administration of single and repeated doses to healthy subjects.

Materials and methods

Subjects

In two separate studies, 16 healthy male subjects (study A) with a mean age of 28 years and mean weight of 76 kg and 16 healthy subjects (8 male and 8 female, study B) with a mean age of 27 years and a mean weight of 72 kg were included. The two studies were conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of the University of Göteborg and the University of Uppsala and by the Swedish Medical Products Agency. Written informed consent was received from all subjects prior to participation.

All subjects underwent a full clinical examination, including past medical history, physical examination and electrocardiogram (ECG) at pre-entry. Laboratory screen for haematology and serum biochemistry was also performed prior to participation in the studies.

Study design

The two studies were conducted according to an open design and each consisted of four investigation days. In studies A and B, subjects received i.v. doses of 20 mg and 40 mg esomeprazole, respectively, on the first investigation day (first i.v). After a washout period of 5–14 days, the same doses (20 mg as a solution and 40 mg as a capsule) were given orally for 5 days and then again intravenously on day 6 (second i.v.). Blood samples for determination of esomeprazole in plasma were taken up to 12 h (study A) or 24 h (study B) post-dose after the first and second i.v. doses and on day 1 and day 5 of oral dosing. Plasma samples for esomeprazole main inactive metabolites were also assessed in study B.

Alcohol intake was not allowed for 2 days prior to or during the treatment period. Drugs available on prescription had not been allowed during the last 2 weeks preceding the studies. Oral contraceptives were not allowed. On the four investigation days, the subjects arrived at the laboratory in the morning, having fasted since the previous evening, for administration of drug and for collection of repeated blood samples. On these days, standardised meals were served 4 (lunch), 7 (light meal), and 10 h (dinner) after drug administration.

Study drugs

For esomeprazole 20 mg, the oral and the i.v. study formulations were present as its corresponding sodium salt in solution, (5 mg/ml, AstraZeneca R and D Mölndal, Sweden). The oral esomeprazole 40 mg was present as its corresponding magnesium salt as enteric-coated pellets dispensed in a hard gelatin capsule, while the i.v. 40 mg formulation was present as its sodium salt in solution, (5 mg/ml, AstraZeneca R and D Mölndal). The concentration of esomeprazole is stated with respect to the neutral form.

For the 20-mg oral dose, 4 ml of the drug solution was diluted with distilled water to a volume of 50 ml and was given to the subject to swallow. The beaker was rinsed twice with 50 ml buffer solution (0.16 mmol/l). For the i.v. 20-mg dose, 4 ml of the solution was added to a 96-ml sodium chloride i.v. infusion to give a final concentration of 0.2 mg/ml esomeprazole. A volume of 100 ml was administered intravenously over 30 min.

The 40-mg capsule was taken orally with 200 ml water. For the i.v. 40-mg dose, 8 ml of the drug solution was added to a 192-ml sodium chloride i.v. infusion to give a final concentration of 0.2 mg/ml esomeprazole. A volume of 200 ml was administered intravenously over 30 min.

Blood sampling

On each of the four investigation days a reference blood sample was drawn from an indwelling cannula in a forearm vein followed by i.v. or oral administration of esomeprazole. The i.v. doses were infused for 0.5 h through a second indwelling cannula. Thereafter, blood samples for the assay of esomeprazole and its metabolites were taken at pre-dose and at 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 or 24 h post-dose, collected in heparinised tubes, centrifuged and the plasma stored frozen until analysis.

In study A (20-mg dose), the plasma samples were analysed for esomeprazole using normal-phase liquid chromatography with ultraviolet (UV) detection at AstraZeneca R and D Mölndal [5]. In study B (40-mg dose), the plasma samples were analysed for esomeprazole and its metabolites (esomeprazole sulphone and 5-hydroxy esomeprazole) using normal-phase liquid chromatography with UV detection with some modifications. The compounds were detected in the elute using UV at 302 nm and the retention times were 3.5, 4.5, 8.0 and 5.5 min, respectively, for esomeprazole, esomeprazole sulphone, 5-hydroxy esomeprazole and the internal standard. The absolute recovery for esomeprazole and the sulphone metabolite at 25–2500 nmol/l was greater than 90% and for the hydroxy metabolite at 50–3000 nmol/l was 70%. The limit of quantification for esomeprazole and esomeprazole sulphone was 25 nmol/l with coefficient of variation (CV) less than 20% and for 5-hydroxy esomeprazole 50 nmol/l (CV < 20%). The plasma samples were analysed for the compounds at AstraZeneca R and D Mölndal.

Pharmacokinetic and statistical analyses

Pharmacokinetic parameters of esomeprazole and its main metabolites, esomeprazole sulphone and 5-hydroxy esomeprazole, were estimated using non-compartment analysis with WinNonlin computer software. The total AUC was calculated according to the log–linear trapezoidal method and extrapolated to infinity using the last determined plasma concentration and λ, which is the elimination rate constant determined using log–linear regression analysis of the terminal slope of at least three last plasma concentration–time data. The terminal plasma elimination half-life ($t_{1/2}$) was calculated as:

$$\frac{\ln 2}{\lambda}$$

The absolute bioavailability (F) of esomeprazole following the oral doses was calculated as:

$$F_{Day1} = \frac{AUC_{po,\,Day\,1}}{AUC_{iv,\,1^{st}dose}} \cdot \frac{Dose_{iv,\,1^{st}dose}}{Dose_{po,\,Day\,1}}$$

$$F_{Day5} = \frac{AUC_{po,\ Day\ 5}}{AUC_{iv,\ 2^{nd}dose}} \cdot \frac{Dose_{iv,\ 2^{nd}dose}}{Dose_{po,\ Day\ 5}}$$

For the oral doses, the observed maximum plasma concentration (C_{max}) as well as the time to reach C_{max} (t_{max}) was also recorded. For the i.v. doses the plasma clearance (CL) of esomeprazole was estimated as $CL = \frac{Dose_{iv}}{AUC_{iv}}$ and the apparent volume of distribution at steady state (V_{ss}) as MRT × CL, where MRT is the mean residence time (AUMC/AUC-T/2). AUMC is the area under the first moment curve and T is the infusion time.

The pharmacokinetic parameters were analysed using a mixed model analysis of variance (ANOVA) with day as a fixed effect and subject as a random effect. Comparisons between the first and second i.v. administrations and between day 1 and day 5 of the oral dosing were performed. The pharmacokinetic parameters were log-transformed prior to the analysis. Estimates and 95% confidence limits of log-transformed parameters were anti-logarithmised, and the results are presented as geometric means and the ratio thereof with confidence intervals.

Results

Intravenous doses of 20 mg or 40 mg

The mean plasma concentrations of esomeprazole after i.v. administration of 20 mg or 40 mg are shown in Fig. 1 and the corresponding pharmacokinetic parameters are presented in Table 1 and Table 2, respectively. The plasma levels were higher after the second i.v. dose than the first dose both after the 20-mg and the 40-mg doses. The CL decreased by 29% after the second 20-mg dose and by 46% after the second 40-mg dose. The $t_{1/2}$ was prolonged by approximately 50% for both doses. The Vss was approximately 18 l for both dose levels and on day 1 and day 5.

Oral doses of 20 mg or 40 mg

The mean plasma concentrations of esomeprazole after oral administration of 20 mg as a solution or 40 mg as a capsule are shown in Fig. 2, and the corresponding pharmacokinetic parameters are presented in Table 1 and Table 2, respectively. The pharmacokinetics for the main metabolites esomeprazole sulphone and 5-hydroxy esomeprazole are shown in Table 3.

Esomeprazole 20 mg given as an oral solution was rapidly absorbed, reaching C_{max} at 0.5 h. The C_{max} for the 40-mg capsule was reached at a later time than the solution but within 1–3.5 h.

The plasma levels of esomeprazole after the 20-mg dose were higher after repeated dosing (day 5) than after a single dose (day 1) as reflected in a 43% higher C_{max} (1.9 μmol/l versus 2.6 μmol/l) and a 90% higher AUC (1.34 μmol × h/l versus 2.55 μmol × h/l). F was 50% on day 1 and 68% on day 5. Following 40-mg oral administration, the C_{max} increased by 95% (2.38 μmol/l versus 4.64 μmol/l) and the AUC by 159% (4.32 μmol × h/l versus 11.21 μmol × h/l) on day 5 compared with day 1. F was 64% on day 1 and 89% on day 5.

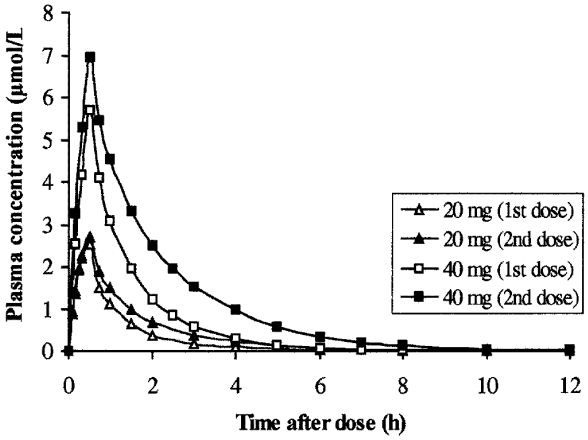

Fig. 1 Mean plasma concentrations of esomeprazole following intravenous administration of 20 mg ($n = 16$ male subjects) or 40 mg ($n = 16$ male and female subjects) as a single dose (1st dose) and after 5 days of oral dosing (2nd dose)

In the investigation of the 40-mg dose of esomeprazole, eight male and eight female subjects participated. Female subjects generally had higher AUC of esomeprazole than male subjects (6.28 μmol × h/l versus 2.97 μmol × h/l) following a single dose of esomeprazole. There was a tendency for a higher AUC (13.37 μmol × h/l versus 9.40 μmol × h/l) following repeated administration but there was no statistically significant difference.

The AUC for the inactive esomeprazole sulphone increased from 4.06 μmol × h/l to 16.17 μmol × h/l from day 1 to day 5, and that for the 5-hydroxy esomeprazole increased from 0.71 μmol × h/l to 0.97 μmol × h/l following repeated oral administration of 40 mg esomeprazole. The $t_{1/2}$ values for the sulphone and 5-hydroxy esomeprazole were prolonged from 2.6 h to 3.8 h and from 1.3 h to 2.2 h, respectively. Esomeprazole, given in daily repeated doses of 20 mg or 40 mg was well tolerated.

Discussion

Esomeprazole 20 mg given as an oral solution was more rapidly absorbed than after 40 mg given as a capsule, which is an expected difference between a capsule formulation and an oral solution. Esomeprazole oral formulations were present as capsules or solution containing different salts (magnesium and sodium salts, respectively). However, since the bioavailability of a capsule formulation of esomeprazole relative to that of a solution containing magnesium and sodium salt, respectively, was complete (AstraZeneca AB, data on file), the different formulations and salts used in esomeprazole in the present investigation are unlikely to have any influence on the results.

Table 1 Pharmacokinetic parameters [geometric mean values with 95% confidence intervals (*95% CI*)] of esomeprazole following intravenous (1st and 2nd doses) and oral (day 1 and day 5) routes of administration of 20 mg esomeprazole to healthy male subjects ($n = 16$). C_{max} observed maximum plasma concentration; $t_{1/2}$ plasma elimination half-life; *CL* plasma clearance; V_{ss} apparent volume of distribution at steady state; *AUC* area under the plasma concentration–time curve; *F* absolute bioavailability

Route	Pharmacokinetic parameter			
Intravenous route	C_{max} (μmol/l)	$t_{1/2}$ (h)	CL (l/h)	V_{ss} (l)
1st dose (95% CI)	2.51 (2.28–2.76)	0.78 (0.62–0.94)	21.7 (17.7–26.8)	17.8 (16.8–18.9)
2nd dose (95% CI)	2.67 (2.43–2.94)	1.15 (0.99–1.31)	15.5 (12.6–19.1)	19.8 (17.0–23.3)
Ratio 2nd dose/1st dose (95% CI)	1.07 (0.99–1.15)	1.56 (1.21–1.91)	0.71 (0.66–0.78)	1.16 (0.93–1.39)
Oral route	C_{max} (μmol/l)	$t_{1/2}$ (h)	AUC (μmol × h/l)	F (%)
Day 1 (95% CI)	1.86 (1.58–2.18)	0.75 (0.58–0.91)	1.34 (1.02–1.77)	50.0 (45.0–56.0)
Day 5 (95% CI)	2.65 (2.26–3.11)	1.01 (0.85–1.18)	2.55 (1.94–3.36)	68.0 (62.0–76.0)
Ratio day 5/day 1 (95% CI)	1.43 (1.23–1.66)	1.36 (1.23–1.49)	1.90 (1.72–2.09)	1.35 (1.23–1.49)

Table 2 Pharmacokinetic parameters [geometric mean values with 95% confidence intervals (*95% CI*)] of esomeprazole following intravenous (1st and 2nd doses) and oral (day 1 and day 5) routes of administration of 40 mg esomeprazole to healthy male and female subjects ($n = 16$). C_{max} observed maximum plasma concentration; $t_{1/2}$ plasma elimination half-life; *CL* plasma clearance; V_{ss} apparent volume of distribution at steady state; *AUC* area under the plasma concentration–time curve; *F* absolute bioavailability

Route	Pharmacokinetic parameter			
Intravenous route	C_{max} (μmol/l)	$t_{1/2}$ (h)	CL (l/h)	V_{ss} (l)
1st dose (95% CI)	5.53 (4.90–6.25)	0.85 (0.74–0.98)	17.05 (13.74–21.14)	17.98 (16.34–19.78)
2nd dose (95% CI)	6.91 (6.36–7.52)	1.22 (1.07–1.38)	9.18 (7.66–11.01)	15.55 (14.71–16.44)
Ratio 2nd dose/1st dose (95% CI)	1.25 (1.16–1.35)	1.43 (1.31–1.57)	0.54 (0.47–0.62)	0.87 (0.82–0.91)
Oral route	C_{max} (μmol/l)	$t_{1/2}$ (h)	AUC (μmol × h/l)	F (%)
Day 1 (95% CI)	2.38 (1.77–3.19)	0.85 (0.73–0.99)	4.32 (3.04–6.14)	63.6 (54.10–74.74)
Day 5 (95% CI)	4.64 (3.80–5.66)	1.25 (1.09–1.44)	11.21 (8.56–14.67)	88.9 (80.8–97.79)
Ratio day 5/day 1 (95% CI)	1.95 (1.59–2.40)	1.48 (1.29–1.69)	2.59 (2.11–3.19)	1.40 (1.23–1.59)

The F of esomeprazole was higher on day 5 than on day 1 following repeated oral administration of 20 mg or 40 mg. The CL of esomeprazole decreased after repeated i.v. dosing of 20 mg or 40 mg and $t_{1/2}$ was prolonged accordingly. The volume of distribution of esomeprazole was approximately 18 l, which equals the volume of extracellular body water, and was not altered by repeated dosing. The increased AUC during repeated dosing with esomeprazole observed here and previously [3] is probably caused by a combination of a decreased first-pass elimination and a decreased systemic clearance.

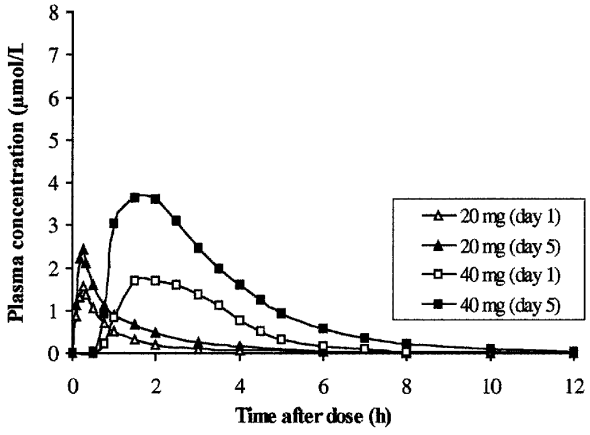

Fig. 2. Mean plasma concentrations of esomeprazole following oral administration of a single dose (day 1) and after five daily doses (day 5) of 20 mg as a solution ($n = 16$ male subjects) or 40 mg as a capsule ($n = 16$ male and female subjects)

In the investigation of the 40-mg dose of esomeprazole, eight male and eight female subjects participated. Female subjects generally had higher AUCs of esomeprazole than male subjects following a single dose. Somewhat higher AUCs, although not statistically significant, were also observed following repeated administration. Esomeprazole is eliminated primarily by hepatic metabolism mediated by CYP2C19 and CYP3A4 [2]. It has previously been shown that female subjects have a higher activity of CYP3A4 than male subjects, while the activity of CYP2C19 is lower [6, 7]. This could possibly be due to the different hormone pattern in females versus males and potential inhibitory effect of the female hormones on CYP2C19. This may also be the reason for a less pronounced increase in AUC observed with repeated dosing in female subjects, since the CYP2C19 activity may be already somewhat inhibited and the influence of an additional inhibitory effect on CYP2C19 would be limited and less than for male subjects. Nevertheless, this gender difference in CYP activity may explain the observed difference in the pharmacokinetics of esomeprazole between males and females in the present investigation.

The plasma levels for the inactive esomeprazole sulphone were substantially higher on day 5 than day 1,

Table 3 Pharmacokinetic parameters [geometric mean values with 95% confidence intervals (*95% CI*)] of esomeprazole sulphone ($n=6$) and 5-hydroxy esomeprazole ($n=15$) following oral (day 1 and day 5) route of administration of 40 mg esomeprazole to healthy male and female subjects. C_{max} observed maximum plasma concentration; $t_{1/2}$ elimination half-life; *AUC* area under the plasma concentration–time curve

Metabolite	Pharmacokinetic parameter		
	C_{max} (μmol/l)	$t_{1/2}$ (h)	AUC (μmol × h/l)
Esomeprazole sulphone			
Day 1 (95% CI)	0.76 (0.52–1.11)	2.55 (2.01–3.24)	4.06 (2.24–7.37)
Day 5 (95% CI)	1.71 (1.30–2.25)	3.84 (3.26–4.51)	16.17 (10.89–24.01)
Ratio day 5/day 1 (95% CI)	2.25 (1.99–2.55)	1.50 (1.29–1.75)	3.98 (3.04–5.20)
5-Hydroxy esomeprazole			
Day 1 (95% CI)	0.29 (0.24–0.34)	1.27 (1.07–1.52)	0.71 (0.58–0.87)
Day 5 (95% CI)	0.28 (0.25–0.31)	2.15 (1.71–2.70)	0.97 (0.80–1.18)
Ratio day 5/day 1 (95% CI)	0.96 (0.82–1.12)	1.72 (1.41–2.09)	1.39 (1.23–1.57)

while those for the inactive 5-hydroxy metabolite were only slightly increased from day 1 to day 5 of repeated oral dosing of 40 mg esomeprazole. The formation of the 5-hydroxy metabolite is dependent on CYP2C19, whereas the formation of the sulphone metabolite is dependent on CYP3A4 [2, 8, 9]. The higher plasma levels for esomeprazole sulphone after repeated dosing of esomeprazole is likely due to an inhibition of its further metabolism which is mediated by CYP2C19. Higher plasma levels for the sulphone metabolite have also been reported after repeated administration of the omeprazole racemate [10].

The CL of esomeprazole was 22 l/h after a single i.v. dose of 20 mg and 17 l/h after a single 40-mg dose. The corresponding values for the same doses of omeprazole racemate, as reported in a previous study, were 28 l/h and 24 l/h, respectively [11]. Thus the CL of esomeprazole seems to be lower than that of the omeprazole racemate. A lower CL of esomeprazole relative to that of omeprazole racemate was also indicated in human liver microsomal experiments with an intrinsic CL for esomeprazole substantially lower than that for *R*-omeprazole (the other isomer) and, consequently, lower than that for the omeprazole racemate [2].

The plasma concentrations of esomeprazole after repeated oral administration of 20 mg were higher, almost twofold, than those observed after repeated oral administration of the same dose of the omeprazole racemate [4]. The major reason for this is a more pronounced increase in AUC for esomeprazole than for omeprazole with repeated dosing. The CL of esomeprazole decreased by 29% and 46% after repeated dosing with 20 mg and 40 mg of esomeprazole, respectively. After 40 mg of omeprazole given repeatedly as i.v. doses over 5 days CL was decreased by 47% [12]. The F of esomeprazole was 50% and 64% after 20-mg and 40-mg single doses, respectively. Previous studies with the omeprazole racemate 20-mg and 40-mg single dose indicate that the bioavailability of the racemate (40%) is slightly lower than that of esomeprazole [11]. The F during repeated dosing of omeprazole racemate, 20 mg daily, approaches 60% [13], which is to be compared with the values of 68% for 20 mg esomeprazole in the present investigation. Thus, both at single-dose and at steady-state conditions, the bioavailability is higher for esomeprazole than for the omeprazole racemate mainly as a consequence of a lower first-pass elimination and lower systemic CL for esomeprazole. The higher bioavailability is likely to provide a rational basis for an increased clinical efficacy of esomeprazole compared with the omeprazole racemate since the effect on gastric acid secretion is correlated to the AUC [14, 15].

The changes in drug exposure after repeated administration of esomeprazole as well as the omeprazole racemate can be due to an inhibition of CYP2C19. An inhibition of CYP2C19 has previously been suggested as the explanation for the findings with the omeprazole racemate, both with regard to the increased AUC of omeprazole itself and the inhibition of the metabolism of diazepam [10]. Strong support for this explanation can be found in the unaltered omeprazole AUC as well as the lack of interaction with diazepam during repeated dosing of the omeprazole racemate in poor metabolisers lacking CYP2C19 [16, 17]. For the metabolism of esomeprazole, CYP2C19 has been shown to play a less dominant role than that for the omeprazole racemate or the other isomer, *R*-omeprazole. CYP3A4 seems to play a relatively more important role for the metabolism of esomeprazole than the racemate [2]. Nevertheless, the present investigation together with previous results seems to indicate that the increase in AUC at repeated dosing is more pronounced for esomeprazole than it is for the omeprazole racemate. One possible explanation is that the increase in AUC from day 1 to day 5 seems to be related to esomeprazole but not to *R*-omeprazole [3]. Finally, it should be noted that because of the threefold difference in AUC of esomeprazole between extensive and poor metabolisers, CYP2C19 is probably responsible for approximately two-thirds of the total metabolism of esomeprazole. Whether an inhibition by CYP2C19 is caused by the esomeprazole or the sulphone metabolite that is further metabolised by CYP2C19 has not been explored. However, the most likely explanation for the increased plasma concentrations obtained during re-

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