DRUG DISPOSITION

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Pharmacokinetic Studies with Esomeprazole, the (*S*)-Isomer of Omeprazole

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Abstract

This article reviews the pharmacokinetics of esomeprazole, the (*S*)-isomer of the proton pump inhibitor (PPI) omeprazole. Esomeprazole is the first single isomer PPI developed for the treatment of patients with acid-related diseases.

In vitro experiments in human liver microsomes demonstrated that the formation of the hydroxy and 5-*O*-desmethyl metabolites of esomeprazole is via cytochrome P450 (CYP) 2C19, whereas that of the sulphone metabolite is via CYP3A4. The formation rate of the hydroxy metabolite from esomeprazole is lower than for (*R*)-omeprazole, but that of the 2 other metabolites is higher, demonstrating stereoselective metabolism. The sum of the intrinsic clearances of all 3 metabo-

lites for esomeprazole was one-third of that for (*R*)-omeprazole, suggesting lower clearance of esomeprazole *in vivo*.

In vivo investigations demonstrated that esomeprazole is chirally stable after administration. Esomeprazole is 97% bound to plasma proteins. In normal (extensive) metabolisers with regard to CYP2C19, esomeprazole is metabolised more slowly than omeprazole, resulting in a higher area under the concentration-time curve (AUC) after administration of the same dose. This is more pronounced after repeated administration rather than after a single dose. In poor metabolisers, the AUC is lower for esomeprazole than for omeprazole, contributing to less overall interindividual variability for esomeprazole than for omeprazole.

In general, esomeprazole and omeprazole are subject to the same metabolic transformations. Almost complete recoveries were reported and the ratio between urinary and faecal excretion is about 4 : 1 for both compounds. The dose-dependent increase in AUC of esomeprazole with repeated administration results from a combination of decreased first-pass elimination and decreased systemic clearance. Patients with gastro-oesophageal reflux disease exhibit a pharmacokinetic pattern similar to that in healthy individuals, whereas elderly individuals exhibited a slightly lower metabolism rate.

Patients with a severe deficit in their liver function had a lower rate of metabolism, as would be expected, whereas those with mild to moderate liver disease did not exhibit any alteration in the pharmacokinetics. The pharmacokinetics of esomeprazole in individuals with impaired renal function is unlikely to differ from that in healthy individuals. A slight sex difference in the pharmacokinetics of esomeprazole was demonstrated in that the AUC and peak plasma drug concentration were slightly, but not statistically significantly, higher in females than in males.

The proton pump (H^+, K^+-ATPase) inhibitor omeprazole is a racemic mixture of the 2 optical isomers (*R*)- and (*S*)-omeprazole (esomeprazole). Like the other proton pump inhibitors (PPIs) lansoprazole, pantoprazole and rabeprazole, omeprazole is a substrate for the polymorphically expressed cytochrome P450 (CYP) enzyme CYP2C19.[1,2] A small proportion of the population (approximately 3% of Caucasians and 15% of Asians) do not express a functional form of this particular enzyme and, hence, these individuals exhibit several-fold higher than average area under the plasma concentration-time curves (AUC) after the administration of these drugs.[3]

The metabolism of omeprazole is stereoselective, and the metabolism rate of the (*S*)-isomer is lower and less variable than that of the (*R*)-isomer, resulting in higher plasma concentrations of the (*S*)-isomer following administration of the same dose.[4,5] Important in this context is that omeprazole and esomeprazole are protonated and converted in the acidic compartment of the parietal cell to form the active inhibitor, the achiral sulphenamide. This structure is identical for the 2 drugs and acts identically on the H^+, K^+-ATPase. This means that the AUC of the drug, irrespective of whether it originates from administered omeprazole or esomeprazole, is correlated to the acid inhibitory effect. Hence, the pharmacokinetic parameter that is best correlated to the acid suppressive effect, the AUC,[6] was almost 2-fold higher after esomeprazole than after an equivalent dose of omeprazole, resulting in a more pronounced acid suppressive effect for esomeprazole, with a longer time with pH > 4.[7] In addition, the time with intragastric pH > 4 was significantly longer for esomeprazole 40mg than for 20mg.

The time with pH > 4 is usually considered to be

correlated with clinical effect on gastric acid-related diseases, and is used as a surrogate endpoint in that respect. Thus, these results were the main reason for the decision to use esomeprazole 40mg in the clinical programme. The advantageous pharmacokinetic profile of esomeprazole compared with omeprazole has been shown to translate into superior efficacy in the clinical situation. In clinical studies, esomeprazole has been shown to be more effective than omeprazole in the treatment of gastro-oesophageal reflux disease (GORD) in patients with erosive oesophagitis, and, in addition, esomeprazole 40mg demonstrated better efficacy than esomeprazole 20mg.[8]

The pharmacokinetics of esomeprazole have been studied after single and repeated administration in healthy individuals as well as in patients with symptomatic GORD, and in special populations, such as patients with hepatic impairment, and elderly, but otherwise healthy, individuals. The potential influence of gender on the metabolism of esomeprazole has also been studied.

1. *In Vitro* Studies

The *in vitro* investigations explored the metabolic routes and mapped which enzymes are responsible for the different transformations of the 2 optical isomers of omeprazole. The plasma protein binding of the 2 optical isomers was also determined with *in vitro* experiments.

1.1 Metabolism in Human Liver Microsomes

The metabolism of esomeprazole and (*R*)-omeprazole were studied using *in vitro* test systems, including human liver microsomes and *in vitro* expressed human CYP isoforms.[4] The rate and extent of formation of the 3 major metabolites, the hydroxy, sulphone and 5-*O*-desmethyl metabolites, were assessed in these systems.

In the first set of experiments, liver tissue from 3 separate livers was used to prepare human liver microsomes for determination of the maximum rate of metabolism (V_{max}) and the Michaelis-Menton constant (Km), which inversely reflects the affinity of drug for enzyme. Intrinsic clearance (CL_{int}) was calculated as the ratio between V_{max} and Km. Stereoselectivity in the metabolism of the 2 optical isomers of omeprazole was clearly demonstrated in these experiments (fig. 1). For (*R*)-omeprazole the dominant metabolic step is the formation of hydroxy-omeprazole, whereas for esomeprazole the formation of each of the 3 metabolites seems to be equally important. Similar affinities of the 2 optical isomers for the enzymes that are responsible for the formation of the 3 metabolites were observed. The highest affinity seemed to be for the enzyme that mediates the formation of the hydroxy metabolite, and the lowest affinity for the enzyme that mediates the formation of the sulphone.

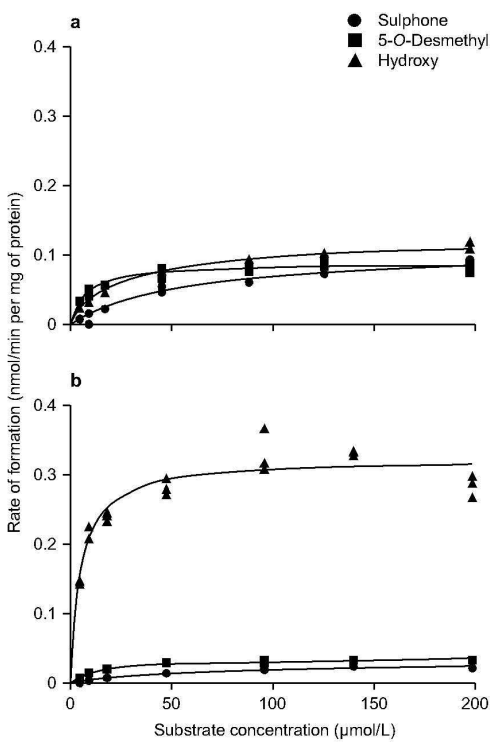

Fig. 1. Formation of the sulphone, hydroxy and 5-*O*-desmethyl metabolites from esomeprazole (**a**) and (*R*)-omeprazole (**b**) in human liver microsomes from one representative liver (HL 102) [this includes new data and data from Äbelö et al.[4]].

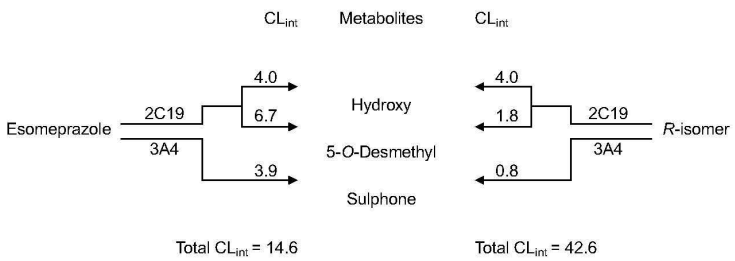

Fig. 2. Metabolism scheme illustrating the intrinsic clearance values (CL_{int}) for the different metabolic pathways of esomeprazole and (*R*)-omeprazole from *in vitro* experiments on human liver microsomes.[4] Values of CL_{int} are expressed as µl/min per mg of protein.

The CL_{int} for the hydroxy metabolite formed from esomeprazole was 10 times lower than that from (*R*)-omeprazole, whereas for the sulphone and 5-*O*-desmethyl metabolites this value was higher. The relative proportion of the sums of the CL_{int} values of all 3 metabolites was 1 : 3 for esomeprazole versus (*R*)-omeprazole (fig. 2), suggesting that esomeprazole would be cleared more slowly than the other optical isomer *in vivo*.

In the second set of experiments, a test kit of human liver microsomal samples from 10 different livers was used in correlation experiments. In these experiments, the rates of formation of the 3 different metabolites of esomeprazole were tested for correlation with the formation rate of metabolites of drugs with a CYP isoform-specific metabolism. Using this method, it is possible to map the metabolic routes of esomeprazole to specific CYP enzymes. The results indicated that the hydroxy as well as the 5-*O*-desmethyl metabolites of both optical isomers are formed mainly by CYP2C19. The sulphoxidation is catalysed by CYP3A4.

Lastly, in the third set of experiments, microsomes from a human lymphoblastoid cell line expressing CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9-Arg, CYP2C19, CYP2D6-Val, CYP2E1 and CYP3A4 were used to determine the kinetic parameters of esomeprazole and (*R*)-omeprazole. Each set of microsomes contains only 1 specific CYP enzyme. The results of the experiments with cDNA-expressed enzymes indicated that the hydroxy as well as the 5-*O*-desmethyl metabolites of both optical isomers are formed mainly by CYP2C19 (Km approximately 5 µmol/L), whereas the sulphoxidation is catalysed by CYP3A4 (Km approximately 80 µmol/L). These results are in agreement with the results of the correlation experiments described above.

It is obvious that the rate at which CYP2C19 forms the hydroxy metabolite from esomeprazole is lower than that from (*R*)-omeprazole, while the rate by which this enzyme forms the 5-*O*-desmethyl metabolite from esomeprazole is higher. It was also shown that the rate at which CYP3A4 forms the sulphone metabolite was higher for esomeprazole than for (*R*)-omeprazole. This is in agreement with the results obtained in the human liver microsomal experiments with the 3 liver samples.

In conclusion, *in vitro* data show that the formation of the hydroxy, sulphone and 5-*O*-desmethyl metabolites of esomeprazole, the 3 major metabolites formed, is mediated via CYP2C19, CYP3A4 and CYP2C19, respectively, for both optical isomers. The affinity for CYP2C19 is approximately 10-fold higher than that for CYP3A4. However, the rate at which the hydroxy metabolite is formed from esomeprazole is lower, and the rate at which the sulphone and 5-*O*-desmethyl metabolites are formed is higher, compared with (*R*)-omeprazole, clearly showing the difference in metabolic profile between the 2 optical isomers. In addition, the sum of the CL_{int} values of all 3 metabolites for esomeprazole was one-third of that for (*R*)-omeprazole, predicting that esomeprazole would be cleared more slowly than (*R*)-omeprazole *in vivo* and, thus,

plasma concentrations would be higher for esomeprazole than for omeprazole.

1.2 Plasma Protein Binding Studies

Plasma from 6 healthy volunteers (3 men and 3 women) was used for individual determinations of the plasma protein binding of esomeprazole, (*R*)-omeprazole and omeprazole, by an ultrafiltration method.[9] The 2 concentrations at which the binding was determined were selected to cover the anticipated therapeutic plasma concentrations in humans (2 to 20 μmol/L). Free compound was separated from protein-bound compound, and concentrations were determined by liquid chromatography. The results showed that the protein binding of esomeprazole, (*R*)-omeprazole and omeprazole are the same (97%), and are independent of sex and concentration in the range studied.

2. *In Vivo* Studies

2.1 Pharmacokinetics of Esomeprazole in Young Healthy Volunteers

The potential for chiral inversion of esomeprazole was investigated *in vivo* (section 2.1.1). One study compared the pharmacokinetics of esomeprazole, (*R*)-omeprazole and omeprazole (see section 2.1.2). In another study, the metabolic and excretory pattern of an oral dose of esomeprazole was compared with that of omeprazole (see section 2.1.3). Complete pharmacokinetic investigations with both intravenous and oral administration have been performed at 2 dose levels, 20mg and 40mg (see section 2.1.4). Finally, the dose dependency in pharmacokinetics was demonstrated in one study using 3 different oral doses of esomeprazole (5, 10 and 20mg) and is presented in section 2.1.5.

2.1.1 Studies on Potential for Inversion

Eight healthy males received a single dose of esomeprazole 40mg as a capsule to determine if administered esomeprazole is chirally stable in humans.[10] Plasma samples were taken up to 8 hours after administration for stereoselective determination of esomeprazole and (*R*)-omeprazole for the calculation of AUC. The plasma profiles are shown in fig. 3. The geometric means with 95% confidence intervals for the AUC of (*R*)-omeprazole and esomeprazole were 0.018 (0.004 to 0.086) μmol · h/L and 4.844 (2.670 to 8.790) μmol · h/L. Thus, the degree of inversion based on the ratio of the AUC of (*R*)-omeprazole and esomeprazole was 0.4%, demonstrating that esomeprazole is chirally stable.

2.1.2 Single and Repeated Administration of Esomeprazole, (R)-Omeprazole and Omeprazole

The pharmacokinetics of esomeprazole, (*R*)-omeprazole and omeprazole were investigated in 9 healthy males, 5 of whom were poor metabolisers (PMs), in a nonblind, randomised, 3-way crossover study consisting of 3 treatment periods.[5] In each treatment period either esomeprazole, (*R*)-omeprazole or omeprazole was given once daily over 7 days. The PMs received doses of 60mg and extensive metabolisers (EMs) received doses of 15mg. The pharmacokinetics were studied on days 1 and 7.

After repeated administration in EMs, the AUC of esomeprazole was 2-fold higher than that of omeprazole, and the AUC of (*R*)-omeprazole was half that of omeprazole (fig. 4 and table I). In the PMs, the pattern was reversed; the plasma concentrations of esomeprazole were lower than those of omeprazole, whereas the plasma concentrations of

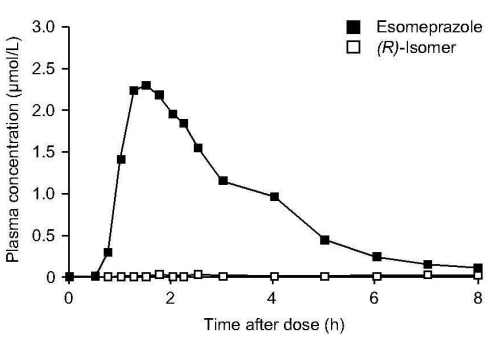

Fig. 3. Mean plasma concentration versus time of esomeprazole and (*R*)-omeprazole following a single oral dose of esomeprazole 40mg as a capsule to 8 healthy males.[10]

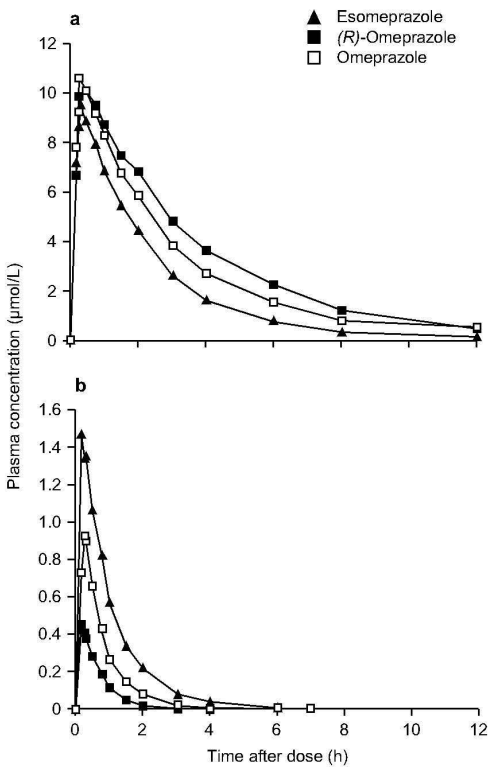

Fig. 4. Mean plasma concentrations versus time of esomeprazole, (*R*)-omeprazole and omeprazole on day 7 of repeated administration of 60mg solutions to (**a**) 5 poor metabolisers and 15mg solutions to (**b**) 4 extensive metabolisers.[5]

(*R*)-omeprazole were higher, resulting in substantially less overall variability for esomeprazole than for omeprazole. There was an increase in the AUC of esomeprazole and omeprazole, but not of (*R*)-omeprazole, in the EMs from day 1 to day 7. This increase was more pronounced with esomeprazole than with omeprazole (112 *vs* 52%). In PMs, no change in AUC was observed during repeated administration for any of the compounds.

2.1.3 Metabolic and Excretory Pattern After a Single Oral Dose

Six healthy males, including 2 PMs, were given single 40mg doses of ^{14}C-labelled esomeprazole and omeprazole, both in aqueous solutions, separated by a wash-out period of at least 2 weeks.[11] In this nonblind, randomised, crossover study the excretion in urine and faeces during a 48-hour period was assessed, and the pharmacokinetics and metabolic patterns of esomeprazole and omeprazole were evaluated.

Both compounds were rapidly absorbed [peak plasma drug concentration (C_{max}) < 0.5 hour, table II]. In EMs, the plasma concentrations of esomeprazole were higher than those of omeprazole. The mean ratio of the AUC values was 1.6, and the mean ratio of the C_{max} values was 1.2. The mean elimination half-life ($t_{½β}$) was 0.9 hours for esomeprazole and 0.7 hours for omeprazole. In the 2 PMs, the plasma concentrations of esomeprazole were lower than those of omeprazole (AUC ratio 0.8), but the C_{max} was approximately the same. The mean $t_{½β}$ was 1.9 hours for esomeprazole and 2.2 hours for omeprazole in the PMs.

The mean recoveries in urine and faeces within 48 hours after the administration of esomeprazole 40mg in the EMs were 77.0% and 18.5% of the dose, respectively (fig. 5). In the PMs the corresponding figures were 72.5% and 22.0%. For omeprazole, in the EMs, the urinary and faecal excretions after 48 hours were 79.5% and 12.4% of the dose, respectively, and in the PMs the corresponding figures were 74.5% and 20.0%. Thus, oral doses of esomeprazole 40mg or omeprazole 40mg were almost completely excreted in urine and faeces with total recoveries of 92% to 96% within 48 hours of administration, and the ratio between urinary and faecal excretion was about 4 : 1 for both compounds in both PMs and EMs.

About 70 metabolites were identified in urine by mass spectrometric detection, whereas radiochemical detection identified only 20 peaks. Of those, 9 were considered major, each constituting >5% and together >59% of the radioactivity excreted within 4 hours after the dose in both EMs and PMs. These metabolites, for example the hydroxy metabolite and its corresponding carboxy metabolite, were formed via different oxidative steps, followed by conjugation with glucuronic acid. Less than 1% of

Table I. Geometric mean pharmacokinetic parameter values (range) on days 1 and 7 of once daily administration of esomeprazole, omeprazole and (*R*)-omeprazole as solutions to poor (60mg) and extensive (15mg) metabolisers

Parameter	Day 1			Day 7		
	esomeprazole	omeprazole	(*R*)-omeprazole	esomeprazole	omeprazole	(*R*)-omeprazole
Extensive metabolisers (n = 4)[a]						
C_{max} (μmol/L)	0.85 (0.20-1.80)	0.57 (0.24-0.94)	0.55 (0.28-0.83)	1.55 (0.89-2.57)	0.88 (0.41-1.43)	0.47 (0.22-0.84)
t_{max} (h)[b]	0.25 (0.17-0.33)	0.28 (0.25-0.33)	0.29 (0.17-0.50)	0.27 (0.17-0.50)	0.29 (0.25-0.33)	0.25 (0.17-0.33)
AUC (μmol • h/L)	0.64 (0.15-1.25)	0.44 (0.18-0.78)	0.34 (0.14-0.51)	1.36 (0.60-2.32)	0.67 (0.25-1.21)	0.31 (0.14-0.47)
$t_{½\beta}$ (h)	0.70 (0.51-0.88)	0.53 (0.41-0.76)	0.44 (0.29-0.54)	0.70 (0.49-1.00)	0.60 (0.48-0.88)	0.42 (0.28-0.52)
Poor metabolisers (n = 5)						
C_{max} (μmol/L)	9.7 (7.6-12.3)	10.5 (7.5-15.4)	12.0 (10.9-13.8)	9.7 (7.8-12.7)	11.0 (9.5-12.7)	10.2 (9.5-11.4)
t_{max} (h)[b]	0.35 (0.17-0.75)	0.23 (0.17-0.33)	0.28 (0.17-0.33)	0.33 (0.17-0.50)	0.33 (0.17-0.50)	0.43 (0.25-0.75)
AUC (μmol • h/L)	22.6 (21.5-24.5)	30.1 (26.3-36.9)	37.9 (31.6-43.2)	21.7 (19.4-24.7)	31.2 (27.3-37.5)	38.1 (32.6-43.5)
$t_{½\beta}$ (h)	1.8 (1.7-2.0)	2.3 (2.2-2.6)	2.5 (2.3-2.7)	1.8 (1.7-1.8)	2.3 (2.2-2.4)	2.4 (2.2-2.8)

a Plasma concentrations of omeprazole in one volunteer were below the limit of quantification at all time-points on day 1 and thus data from this volunteer were not included in the calculations.

b Arithmetic mean.

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma drug concentration; $\mathbf{t_{max}}$ = time to reach peak concentration following drug administration; $\mathbf{t_{½\beta}}$ = elimination half-life.

the parent compound was found in urine. Metabolic patterns in plasma were less complex, with only 4 to 7 metabolites detected. The sulphone metabolite, which was not found in urine, was an important metabolite in plasma. Other major metabolites in plasma, for example, the 5-*O*-desmethyl metabolite, were also found in significant amounts in urine. However, none of these metabolites have been found to be active.

In conclusion, the main differences in pharmacokinetics between esomeprazole 40mg and omeprazole 40mg are that the AUCs for esomeprazole in EMs are 60% higher and those in PMs are 20% lower than for omeprazole. Thus, there is less difference in plasma concentrations between EMs and PMs for esomeprazole than for omeprazole. This demonstrates a lower influence of CYP2C19 on the metabolism of esomeprazole as compared with omeprazole. Also, the data imply that there are no major differences in excretion routes and recoveries following oral administration of esomeprazole or omeprazole in humans.

2.1.4 Single and Repeated Administration of Intravenous and Oral Doses

The pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy individuals were investigated in 2 separate studies.[12] In the first study, a solution of esomeprazole 20mg was administered both orally and intravenously to 16 males. In the second study a 40mg dose was administered both orally, as enteric coated granules in capsules, and intravenously to 8 males, 8 females not using oral contraceptives and 8 females using oral contraceptives. The 2 studies were performed as nonblind,

Table II. Geometric mean pharmacokinetic parameter values (range) after a single oral dose of 40mg of ^{14}C-labelled esomeprazole and omeprazole as solutions in extensive and poor metabolisers

Parameter	Esomeprazole	Omeprazole
Extensive metabolisers (n = 4)		
C_{max} (μmol/L)	5.39 (3.34-7.88)	4.47 (1.88-8.67)
t_{max} (h)[a]	0.29 (0.25-0.33)	0.25 (0.17-0.50)
AUC (μmol • h/L)	5.59 (3.74-9.60)	3.47 (1.74-6.16)
$t_{½\beta}$ (h)	0.86 (0.69-1.37)	0.67 (0.52-0.95)
Poor metabolisers (n = 2)		
C_{max} (μmol/L)	7.83 (6.60-9.30)	7.49 (6.82-8.22)
t_{max} (h)[a]	0.29 (0.25-0.33)	0.34 (0.17-0.50)
AUC (μmol • h/L)	17.0 (16.8-17.3)	20.7 (20.2-21.3)
$t_{½\beta}$ (h)	1.87 (1.85-1.90)	2.15 (1.99-2.34)

a Arithmetic mean.

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma drug concentration; $\mathbf{t_{max}}$ = time to reach peak concentration following drug administration; $\mathbf{t_{½\beta}}$ = elimination half-life.

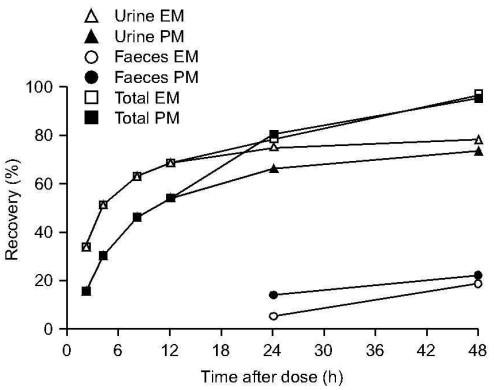

Fig. 5. Mean cumulative excretion of total radioactivity (% recovery of dose) after administration of a single oral dose of ^{14}C-labelled esomeprazole as a solution to poor (PM) and extensive (EM) metabolisers.[11]

1-way trials with a once daily oral dose of esomeprazole given to each participant for 5 days. A single intravenous dose of esomeprazole was administered to each individual 5 to 14 days before the first oral dose, and 1 day after the last oral dose. Blood samples for pharmacokinetic evaluation were taken on days 1 and 5 of oral administration and on the days of intravenous administration.

In the 20mg study using the oral solution, there was rapid absorption after both single and repeated doses and C_{max} was reached within 0.5 hour (fig. 6 and table III). For repeated doses, the AUC of esomeprazole after oral administration increased by 90%, and C_{max} increased by 43%, compared with single dose values. The systemic bioavailability (F) increased from 50% after a single dose to 68% after repeated doses. Following the intravenous doses, the total body clearance (CL) was 29% lower after the second dose than after the first dose and the $t_{½\beta}$ was longer, 1.2 versus 0.8 hours.

In the study using the 40mg capsule formulation, C_{max} was reached later than for the solution (within 1.5 to 2 hours) [table IV]. For the 40mg dose, a more pronounced increase in AUC of esomeprazole with repeated doses was observed than for the 20mg dose, and for the group of males together with females not using oral contraceptives the increase was 159% from day 1 to day 5. Also, there was a near doubling of the C_{max}. The absolute bioavailability increased from 64 to 89% during repeated administration, which not only shows a higher bioavailability for the 40mg dose than for the 20mg dose but also indicates a more pronounced increase with repeated administration of the higher dose.

Following intravenous administration the CL was 17.0 L/h after the first dose and 9.2 L/h after the second dose. This decrease in CL of 46% is to be compared with the 29% decrease in CL observed following the 20mg dose. These results indicate a

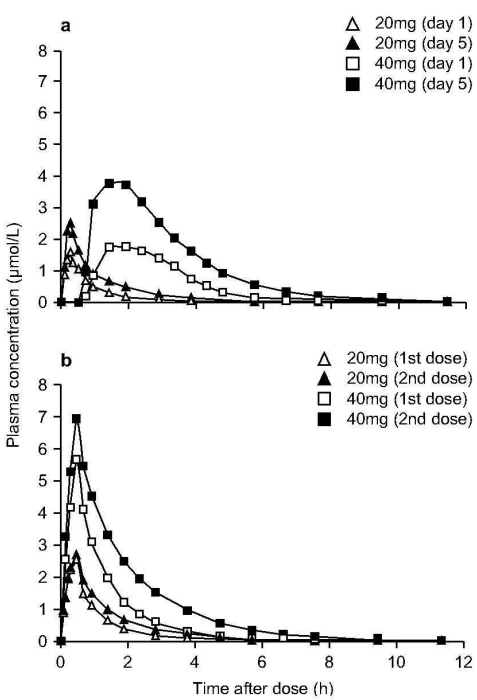

Fig. 6. Mean plasma concentrations versus time after oral administration of single and repeated 20mg (solution) and 40mg (capsules) doses of esomeprazole in 16 healthy males and 16 healthy males and females, respectively (**a**) and mean plasma concentrations over time after first and second intravenous administration of esomeprazole 20mg and 40mg in 16 healthy males and 16 healthy males and females (**b**), respectively (from Hassan-Alin et al.,[12] with permission).

Table III. Geometric mean (95% confidence interval) pharmacokinetic parameter values after single and repeated oral (solution) and intravenous doses of esomeprazole 20mg in 16 healthy males

Parameter	Oral			Intravenous		
	day 1	day 5	day 5/day 1	1st dose	2nd dose	2nd dose/1st dose
C_{max} (μmol/L)	1.86 (1.58-2.18)	2.65 (2.26-3.11)	1.43 (1.23-1.66)			
t_{max} (h)[a]	0.26 (0.17-0.35)	0.21 (0.18-0.25)	–0.05 (–0.14 to 0.04)			
AUC (μmol • h/L)	1.34 (1.02-1.77)	2.55 (1.94-3.36)	1.90 (1.72-2.09)	2.67 (2.20-3.23)	3.74 (3.00-4.68)	1.40 (1.29-1.52)
$t_{½β}$ (h)	0.72 (0.61-0.83)	0.96 (0.80-1.14)	1.34 (1.23-1.47)	0.75 (0.65-0.86)	1.11 (0.95-1.29)	1.48 (1.26-1.74)
F (%)	50 (45-56)	68 (62-76)	1.35 (1.23-1.49)			
CL (L/h)				21.7 (17.7-26.8)	15.5 (12.6-19.1)	0.71 (0.66-0.78)
V_{ss} (L/kg)				0.24 (0.22-0.25)	0.26 (0.23-0.30)	1.12 (0.98-1.27)

a Arithmetic mean with difference between day 5 and day 1 in last column.

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma drug concentration; **F** = bioavailability; **t_{max}** = time to reach peak concentration following drug administration; **$t_{½β}$** = half-life; **V_{ss}** = volume of distribution at steady state.

more pronounced effect of repeated administration of the higher dose, not only on bioavailability but also on systemic clearance. This was also reflected in a prolonged $t_{½β}$, from 0.8 hours after the first dose to 1.2 hours after the second dose.

Similar to the results of the 20mg study, the results of the 40mg study indicate that the increased AUC observed after repeated doses of esomeprazole is because of a combination of decreased first-pass elimination and decreased systemic clearance. However, there is a more pronounced decrease in these parameters with the higher dose, which is reflected in the more pronounced increase in AUC.

In the 40mg study, a separate comparison of the values for the different pharmacokinetic parameters was done for males versus females not using oral contraceptives. The values observed in females not using oral contraceptives were also compared with those in females using oral contraceptives. Oral contraceptives had no major impact on the pharmacokinetics of esomeprazole after single or repeated doses of the compound, following either oral or intravenous administration. The differences between the sexes in the pharmacokinetics of esomeprazole are discussed in section 2.3.3.

2.1.5 Single and Repeated Administration of Different Oral Doses

The pharmacokinetics after a single oral dose and after 5 days repeated administration of solutions of 5, 10 and 20mg of esomeprazole and an enteric-coated granule formulation of omeprazole 20mg in a capsule were assessed in 12 healthy males.[13] This study was a nonblind, randomised,

Table IV. Geometric mean (95% confidence interval) pharmacokinetic parameter values after single and repeated oral (capsule) and intravenous administration of esomeprazole 40mg in 16 healthy males and females

Parameter	Oral			Intravenous		
	day 1	day 5	day 5/day 1	1st dose	2nd dose	2nd dose/1st dose
C_{max} (μmol/L)	2.38 (1.77-3.19)	4.64 (3.80-5.66)	1.95 (1.59-2.40)			
t_{max} (h)[a]	2.06 (1.69-2.43)	1.50 (1.26-1.74)	–0.56 (–0.98 to –0.14)			
AUC (μmol • h/L)	4.32 (3.04-6.14)	11.21 (8.56-14.67)	2.59 (2.11-3.19)	6.84 (5.53-8.46)	12.61 (10.52-15.11)	1.84 (1.61-2.11)
$t_{½β}$ (h)	0.85 (0.73-0.99)	1.25 (1.09-1.44)	1.48 (1.29-1.69)	0.85 (0.74-0.98)	1.22 (1.07-1.38)	1.43 (1.31-1.57)
F (%)	64 (54-75)	89 (81-98)	1.40 (1.23-1.59)			
CL (L/h)				17.0 (13.7-21.0)	9.2 (7.7-11.0)	0.54 (0.47-0.62)
V_{ss} (L/kg)				0.25 (0.23-0.27)	0.22 (0.21-0.23)	0.87 (0.82-0.91)

a Arithmetic mean with difference between day 5 and day 1 in last column.

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma drug concentration; **F** = bioavailability; **t_{max}** = time to reach peak concentration following drug administration; **$t_{½β}$** = elimination half-life; **V_{ss}** = volume of distribution at steady state.

Table V. Geometric mean (95% confidence interval) pharmacokinetic parameter values on days 1 and 5 of oral administration of different doses of esomeprazole as a solution or omeprazole 20mg as a capsule in 12 healthy males

Parameter	Esomeprazole			Omeprazole 20mg
	5mg	10mg	20mg	
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)[a]	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)
$t_{½β}$ (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)[a]	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)
$t_{½β}$ (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)[b]	0.00 (–0.14 to 0.14)	0.04 (–0.07 to 0.16)	–0.08 (–0.16 to –0.01)	–0.71 (–1.14 to –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)
$t_{½β}$	1.17 (1.04-1.32)	1.18 (1.07-1.30)	1.49 (1.28-1.74)	1.12 (0.80-1.57)

a Arithmetic mean.

b Difference between day 5 and day 1.

AUC = area under the plasma concentration-time curve; C_{max} = peak plasma drug concentration; t_{max} = time to reach peak concentration following drug administration; $t_{½β}$ = elimination half-life.

crossover trial, consisting of four 5-day study periods, each separated by a wash-out period of at least 2 weeks.

The AUC of esomeprazole increased proportionally to the dose on day 1, but on day 5 the increases were higher than would be expected from an increase in dose only (table V). This is explained by the fact that the AUC values increase dose-dependently during repeated administration. The increases during repeated administration of 5, 10 and 20mg doses were 14, 51 and 111%, respectively. The AUC of omeprazole increased by 49% during repeated administration of 20mg. Following 20mg doses of both compounds, the AUC at steady state for esomeprazole was approximately 70% higher than that for omeprazole. This is because the AUC was 18% higher on day 1 and the increase from single to repeated doses was more pronounced for esomeprazole than for omeprazole.

According to the studies presented in section 2.1.4,[12] including both oral and intravenous administration, the reason for the higher AUC is a combination of decreased first-pass metabolism and decreased systemic clearance.

2.2 Pharmacokinetics of Esomeprazole in Patients with Symptomatic Gastro-Oesophageal Reflux Disease

Patients with symptoms of GORD are an important target population for esomeprazole. In a group of symptomatic GORD patients recruited to investigate the effect on pH of 2 different doses of esomeprazole, the pharmacokinetics of esomeprazole were evaluated as a secondary objective.[7]

The pharmacokinetic profile of esomeprazole following repeated administration of 20 and 40mg capsules (enteric-coated) to 36 patients (mean age 45 years, 22 females) with symptomatic GORD (30 *Helicobacter pylori*-negative and 6 *H. pylori*-positive), was investigated and compared with the profile observed following treatment with omeprazole 20mg capsules in a double-blind, randomised, 3-way crossover study.[7] Patients received 5 days of once daily oral treatment with each of the 3 study

regimens with each dose taken 30 minutes prior to breakfast. Each treatment period was separated by at least a 2-week washout period. Blood samples were obtained on day 5 of each treatment period for determination of plasma concentrations of esomeprazole or omeprazole.

Esomeprazole was absorbed rapidly, with C_{max} occurring 1.3 to 1.4 hours after administration (fig. 7 and table VI). Although C_{max} on day 5 appeared to increase proportionally to the dose of esomeprazole (20 or 40mg), there was a disproportionate increase in AUC values. The AUC for the 40mg dose was 3-fold higher than for the 20mg dose. Also, confirming observations in healthy volunteers, the AUC for esomeprazole 20mg was approximately 80% higher than that observed for the same dose of omeprazole and the $t_{½\beta}$ for esomeprazole was longer than for omeprazole. The interpatient variability in AUC was lower with esomeprazole 20mg (maximum : minimum ratio of about 17) than with omeprazole 20mg (maximum : minimum ratio of about 46).

It was concluded that the pharmacokinetic profile of esomeprazole in patients with GORD is similar to the profile in healthy individuals.

2.3 Pharmacokinetics of Esomeprazole in Special Populations

Since esomeprazole is completely eliminated from plasma by metabolism in the liver, it was considered important to study the pharmacokinetics in patient groups that may have a decreased function of this organ – patients with liver disease and to some degree elderly patients. The kidney is responsible for the majority of the excretion of metabolites, which are inactive, but not for the elimination from plasma of the parent compound. It has been documented that the pharmacokinetics of omeprazole in patients with renal impairment do not differ from those observed in healthy individuals, but the renal excretion of metabolites was decreased.[14] It was considered unnecessary to duplicate this investigation by performing such a study with esomeprazole.

In addition, the study presented in section 2.1.3 demonstrated that there were no major differences in excretion routes and recoveries following oral doses of esomeprazole and omeprazole in humans. Finally, a pooled analysis with regard to potential gender differences in the pharmacokinetics of esomeprazole is presented in section 2.3.3. The analysis was performed using AUC and C_{max} values obtained in 12 separate clinical pharmacological studies.

2.3.1 Single and Repeated Oral Administration in Healthy Elderly Individuals

Fourteen elderly (mean age 74 years) healthy volunteers, of whom 8 were females, participated in this nonblind, 1-way study consisting of 5 days of oral treatment with daily doses of esomeprazole 40mg as the capsule formulation.[15] The pharmacokinetics were assessed on days 1 and 5.

The time to reach C_{max} (t_{max}) was 1.5 to 2 hours, which is similar to that previously reported in young healthy volunteers (fig. 8 and table VI). The AUC of esomeprazole was 8.25 μmol · h/L on day 1, but increased to 16.0 μmol · h/L on day 5, i.e. an increase of 94%. The C_{max} increased by 52% during repeated administration. The $t_{½\beta}$ was somewhat prolonged with repeated doses, from 1.3 to 1.7 hours. In general, these changes with repeated administration were of the same magnitude as

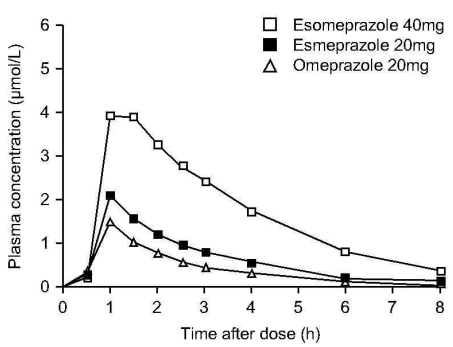

Fig. 7. Mean plasma concentrations versus time after 5 days with esomeprazole 20mg or 40mg as a capsule or omeprazole 20mg in 36 patients with symptomatic gastro-oesophageal reflux disease (from Lind et al.,[7] with permission).

Table VI. Summary table of pharmacokinetic parameters (geometric means with 95% confidence intervals for C_{max}, AUC and $t_{½β}$, and arithmetic means with 95% confidence intervals for t_{max}) during repeated administration of esomeprazole 40mg in different populations

Population	C_{max} (μmol/L)	t_{max} (h)	AUC (μmol • h/L)	$t_{½β}$ (h)	Comments
Young healthy volunteers[12]	4.64 (3.80-5.66)	1.50 (1.26-1.74)	11.2 (8.56-14.7)	1.25 (1.09-1.44)	F = 89%
Females/males[14] ratio	1.14 (1.02-1.27)	NC	1.13 (0.98-1.31)	NC	AUC 13% higher in females
Patients with GORD[7]	4.76 (4.12-5.50)	1.56 (1.30-1.82)	12.6 (9.89-16.2)	1.54 (1.38-1.71)	AUC similar to young healthy volunteers
Elderly healthy volunteers[15]	5.57 (4.71-6.58)	1.50 (1.20-1.80)	16.0 (12.8-20.0)	1.67 (1.42-1.96)	AUC 25% higher than in patients with GORD
Patients with hepatic impairment[16]	6.09 (4.95-7.50)	1.92 (1.46-2.38)	23.1 (18.8-28.4)	2.11 (1.55-2.89)	AUC 76% higher than in patients with GORD

AUC = area under the plasma concentration-time curve; **C_{max}** = peak drug plasma concentration; **F** = bioavailability; **GORD** = gastro-oesophageal reflux disease; **NC** = not calculated; **$t_{½β}$** = elimination half-life; **t_{max}** = time to reach peak plasma concentration.

those previously reported in young healthy individuals.

There were no major differences in any of the pharmacokinetic parameters between males and females in this population of healthy elderly people. The values of AUC and C_{max} in the elderly on day 5 in this study were compared with those from the previously presented study in GORD patients with a mean age of 45 years (section 2.2), who also received 40mg doses of esomeprazole over a 5-day period. The ratio of the mean AUC in the elderly, relative to that in patients with GORD, was 1.25 [95% confidence interval (CI) 0.94 to 1.67]. The corresponding ratio for C_{max} was 1.18 (0.91 to 1.52). These small differences in AUC and C_{max} were not statistically significant, but suggest that the metabolic rate is slightly decreased in the elderly as compared with young and middle-aged individuals. However, the results do not suggest any need for dosage adjustment in elderly patients.

2.3.2 Repeated Oral Administration in Patients with Impaired Liver Function

The pharmacokinetics in 12 individuals, 4 in each class of liver disease as defined by the Child-Pugh scale (A, B and C, corresponding to mild, moderate and severe liver disease, respectively) and with a mean age of 50 years, were assessed on day 5 of 5 days of oral treatment with esomeprazole 40mg daily (capsule form).[16]

The t_{max} was approximately 2 hours, indicating that the time for absorption is similar to that previously reported in healthy young and elderly individuals (fig. 9 and table VI). The AUC of esomeprazole was 23.1 μmol • h/L and the C_{max} was 6.1 μmol/L. The $t_{½β}$ was 2.1 hours. Both esomeprazole and the hydroxy metabolite were undetectable in plasma 24 hours after administration, or earlier, whereas the sulphone metabolite was detectable. However, the same concentrations of sulphone were observed at the time of drug administration on day 5 and 24 hours later, which clearly shows that there is no accumulation of this metabolite during repeated administration of esomeprazole for 5 days or more.

The values of AUC and C_{max} in these individuals with impaired hepatic function were compared with those obtained from the previously presented study in patients with GORD (section 2.2). The metabolic rate is on average lower in individuals with impaired

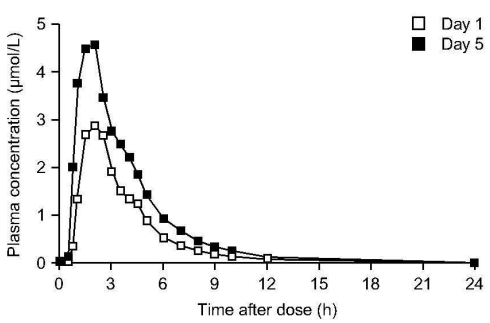

Fig. 8. Mean plasma concentrations versus time of esomeprazole following oral doses of esomeprazole 40mg as a capsule on day 1 (n = 14) and day 5 (n = 13) to elderly males and females (from Hasselgren et al.[15]).

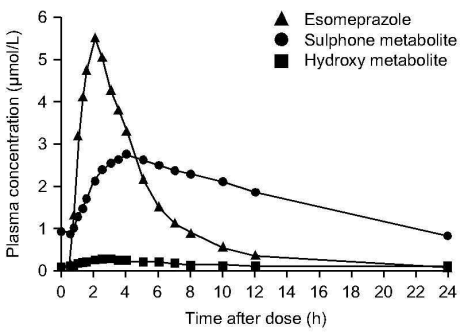

Fig. 9. Mean plasma concentrations versus time of esomeprazole and its hydroxy and sulphone metabolites on day 5 following daily oral doses of esomeprazole 40mg as a capsule to 12 patients with liver dysfunction.[16]

hepatic function. The ratio of the mean AUC in the hepatically impaired patients relative to the patients with GORD was 1.76 (95% CI 1.29 to 2.42). The corresponding ratio for C_{max} was 1.26 (0.94 to 1.69) and for $t_{½\beta}$ it was 1.29 (0.99 to 1.68). However, in the patients with mild and moderate liver disease the metabolic rate did not seem to differ from that in patients with GORD, whereas in the 4 patients with severely impaired hepatic function the metabolic rate was substantially lower (fig. 10). Therefore, no dosage reductions are recommended unless patients have severely impaired liver function, where 20mg daily is likely to be sufficient.

2.3.3 Single and Repeated Oral Administration, Pooled Data from Females Versus Males

Data from 12 studies were pooled to assess differences in AUC and C_{max} between males and females.[17] All values for AUC and C_{max} were calculated following oral administration of esomeprazole 40mg during fasting conditions. Results from only single doses were obtained in 4 studies, from repeated doses in 3 studies, and from both single and repeated doses in 5 studies. The results of the analysis with all studies included suggest that there is a gender difference in these two pharmacokinetic parameters. The values are higher in females, with less difference during repeated administration (table VI). The estimate of the gender effect was approximately the same when studies including only males were excluded. The AUC and C_{max} values were approximately 30% higher in females than in males after single dose administration, whereas at steady state the difference was only 13 to 14% and not statistically significant.

A possible explanation for the overall higher AUC and, hence, slightly delayed elimination in females versus males may be that certain CYP isoforms have different activities in females versus males. It has previously been shown that females have a higher activity of CYP3A4 than males, whereas the activity of CYP2C19 is lower,[18] and these are the 2 enzymes mainly involved in the metabolism of esomeprazole. Other possible explanations may be differences in bodyweight or volumes of distribution.

3. Discussion and Clinical Relevance

The most important finding is that esomeprazole is metabolised more slowly than omeprazole, whereas (*R*)-omeprazole, the other optical isomer, is metabolised more rapidly than omeprazole in EMs. For the majority of the population, this property results in a higher and less variable AUC for esomeprazole than for omeprazole and, in particular, for (*R*)-

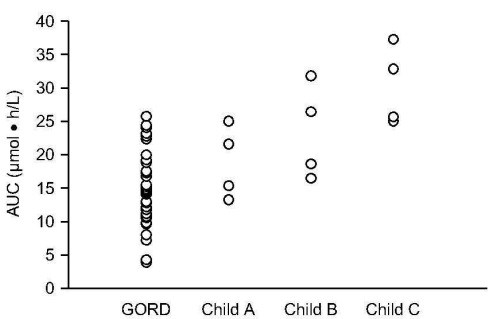

Fig. 10. Individual values for the area under the plasma concentration-time curve (AUC) of esomeprazole in patients with gastro-oesophageal reflux disease (GORD) without liver dysfunction and patients with liver dysfunction grouped according to the degree of liver dysfunction as defined by the Child-Pugh scale (Child A, B, C corresponds to mild, moderate and severe liver disease, respectively).[16] Esomeprazole 40mg, in capsule form, was administered to all participants.

omeprazole, after administration of the same dose of each compound. This is more pronounced after repeated doses than after a single dose, which is a consequence of the more pronounced increase in AUC with repeated doses for esomeprazole than for omeprazole. The AUC of (*R*)-omeprazole did not change with repeated administration. Thus, not only is the metabolic rate of esomeprazole lower than that of omeprazole after a single dose, but the decreased rate of metabolism with repeated doses is more pronounced for esomeprazole.

These are the 2 mechanistic explanations for why the AUC of esomeprazole after repeated doses is 70 to 90% higher than that of omeprazole after doses of 15mg to 20mg.[5,11,13] Only single dose data are available for the 40mg dose and, in that comparison, the AUC for esomeprazole was approximately 60% higher than that for omeprazole.[11]

Another important pharmacokinetic difference between esomeprazole and omeprazole is that the AUC in PMs is slightly lower for esomeprazole than for omeprazole, resulting in less interindividual variability overall in this parameter for esomeprazole than for omeprazole.[5,11] In addition, since the PMs already have AUCs which are higher than needed for the treatment of their disease, it can be considered rather as an advantage to somewhat decrease the drug exposure in those individuals by treating them with esomeprazole instead of omeprazole.

In this review there are 2 studies including both PMs and EMs; in one the EMs received 15mg of esomeprazole while the PMs received 60mg, and in the other esomeprazole 40mg was administered as a single dose. Thus this review does not contain a study where both EMs and PMs were given esomeprazole 40mg repeatedly, which would be the relevant situation to do a comparison on exposure in PMs versus EMs. However, a bioequivalence study was performed in which both EMs and PMs were given esomeprazole 40mg repeatedly, both in the capsule form and a 'multiple unit pellet system' - tablet.[19]

In that study[19] the ratio of esomeprazole AUC in PMs (n = 4) to that in EMs (n = 32) was 1.88, demonstrating a less than 2-fold difference in AUC between EMs and PMs. This in itself would not suggest a dose reduction in PMs especially since the AUC in PMs after esomeprazole 40mg is actually lower than the AUC after omeprazole 40mg, an omeprazole dose that is frequently used in the clinical arena.

Moreover, it would not be feasible to reduce the dose in PMs, since one would then have to genotype or phenotype all patients prior to treatment. Finally, the most obvious reason why the dose would not have to be reduced in PMs, is that no dose-related adverse effects have been reported for either omeprazole or esomeprazole.

The decreased metabolic rate of esomeprazole resulting in the increased AUC of esomeprazole with repeated doses has been shown to be because of a combination of decreased first-pass elimination and decreased systemic clearance. These parameters are influenced dose-dependently, in that the relative changes in absolute bioavailability and clearance are more pronounced with a 40mg dose than with a 20mg dose. A likely explanation for the decreased first-pass elimination and decreased systemic clearance is competitive inhibition of the major esomeprazole metabolising enzyme, CYP2C19, either by esomeprazole itself, or more likely, by the sulphone metabolite which has been demonstrated to inhibit the CYP2C19-mediated hydroxylation and demethylation steps.[20] Support for this explanation can be found in the fact that in PMs, who lack CYP2C19, the AUC does not increase with repeated doses (see section 2.1.2).

The pharmacokinetics of esomeprazole were the same in patients with GORD as in healthy volunteers, whereas elderly individuals had a slightly decreased metabolic rate. Patients with a severe deficit in their liver function exhibited a lower metabolic rate. The slight sex difference in the pharmacokinetics of esomeprazole, reflected in the somewhat higher AUC and C_{max} in females than in males after a single dose, was not statistically significant at steady state.

4. Conclusions

For both optical isomers of omeprazole, esomeprazole and (*R*)-omeprazole, the formation of the hydroxy and 5-*O*-desmethyl metabolites is via CYP2C19, whereas that of the sulphone is via CYP3A4. The rate of formation of the hydroxy metabolite from esomeprazole is lower, and that of the 2 other metabolites is higher, compared with (*R*)-omeprazole, demonstrating stereoselective metabolism. The sum of the intrinsic clearance values for the formation of all 3 metabolites was 3 times lower for esomeprazole than for (*R*)-omeprazole, indicating that esomeprazole would be cleared more slowly *in vivo*. Esomeprazole is 97% bound to plasma proteins.

Esomeprazole is chirally stable *in vivo*. In normal (extensive) metabolisers, esomeprazole is metabolised more slowly than omeprazole, resulting in a higher and less variable AUC of esomeprazole than of omeprazole after administration of the same dose. This is more evident after repeated doses than after a single dose, since there is a more pronounced increase in AUC with repeated administration for esomeprazole than for omeprazole.

The AUC in PMs is lower for esomeprazole than for omeprazole, contributing to less overall interindividual variability for esomeprazole than for omeprazole. In contrast, the AUC of (*R*)-omeprazole in PMs is higher than that of omeprazole.

Esomeprazole and omeprazole are subject to the same structural transformations in general. Almost complete recoveries were reported and the ratio between urinary and faecal excretion is about 4 : 1 for both compounds in both PMs and EMs. The increased AUC of esomeprazole with repeated doses is due to a combination of decreased first-pass elimination and decreased systemic clearance, and these parameters are influenced dose-dependently.

Patients with GORD exhibit a similar pharmacokinetic pattern as healthy individuals, whereas the elderly have a slightly lower metabolic rate. Patients with a severe deficit in their liver function had a lower metabolic rate. The pharmacokinetics of esomeprazole in individuals with impaired renal function are unlikely to differ from those in healthy individuals.

A slight, but not statistically significant, sex difference in the pharmacokinetics of esomeprazole was demonstrated, in that the AUC and C_{max} were slightly higher in females than in males.

Acknowledgements

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