Therapeutic Drug Monitoring
12:163–172 © 1990 Raven Press, Ltd., New York

The Pharmacokinetics of Omeprazole in Humans—A Study of Single Intravenous and Oral Doses

C. G. Regårdh, T. Andersson, P. O. Lagerström, P. Lundborg, and I. Skånberg

Hässle Research Laboratories, Mölndal, Sweden

Summary: The pharamacokinetics of omeprazole, hydroxyomeprazole, omeprazolesulfone, and "remaining metabolites" have been studied in eight young healthy subjects following an acute i.v. and oral dose of 10 and 20 mg of ^{14}C-labeled drug, respectively. The oral dose was given as a buffered solution. Two subjects exhibited essentially higher and more sustained plasma levels of omeprazole than the others. This was due to a higher bioavailability, lower clearance, and longer $t_{1/2}$ of omeprazole in these two subjects. Maximum concentration (0.7–4.6 μmol/L) was reached between 10 and 25 min after oral dosing. The median bioavailability was 39% (25–117%) and the median systemic plasma clearance was 624 ml/min (range of 59–828 ml/min). The corresponding $t_{1/2}$ for the i.v. dose was 35 min (16–150 min) and 39 min (14–186 min) after oral administration. The drug was rapidly distributed to extravascular sites (mean $t_{1/2\lambda 1}$ = 3.0 ± 0.8 min). Mean V_{ss} was 0.23 ± 0.04 L/kg. Low systemic clearance of omeprazole was associated with a decreased formation rate of hydroxyomepraxole and "remaining metabolites" while omeprazolesulfone formation seemed to be less affected. However, there was a clear-cut correlation between the $t_{1/2}$ of omeprazole and of its omeprazolesulfone metabolite, indicating that the elimination of these two compounds is mediated by the same isoenzyme. The mean urinary recovery of the radioactive dose during 96 h was 78.3 ± 2.3 and 75.7 ± 2.6% for the i.v. and oral dose, respectively. Insignificant amounts were due to unchanged drug and omeprazolesulfone. The excretion of hydroxyomeprazole during the first 12 h varied between 4.6 to 15.5% of a given dose. The mean recovery of radioactivity in the feces was 19.3 ± 3.1% of a given i.v. dose and 18.2 ± 2.3% when given orally. It is concluded that omeprazole is mainly eliminated metabolically and that there is a substantial interindividual variation in the rate of formation of primary and secondary metabolites. This variation in omeprazole disposition is probably of limited clinical importance. The half-life, with a maximum of ~3 h, is too short to cause accumulation when the drug is administered in a once-daily regimen.
Key Words: Omeprazole—Disposition—Genetic influence—Metabolism—Individual variation.

Omeprazole (Losec) is a substituted 2-pyridinyl-2-sulfinylbenzimidazole that effectively suppresses gastric acid secretion in the rat, dog, and humans (1,2). The clinical test program has documented that omeprazole is superior to cimetidine and ranitidine in the healing of duodenal ulcers (3–5). Similar findings have been reported in comparative clinical studies of the effect of omeprazole and the H_2-blockers in gastric ulcer and reflux esophagitis (6–9). Outstanding results have been achieved with omeprazole in Zollinger–Ellison patients (10,11).

Received June 20, 1989; accepted October 17, 1989.
Address correspondence and reprint requests to Dr. C. G. Regårdh at Hässle Research Laboratories, S-431 83 Mölndal, Sweden.

Mechanistically, omeprazole differs from the H_2-receptor blockers by selectively inhibiting the enzyme H^+, K^+–ATPase, the proton pump of the gastric mucosa (12,13).

The pharmacokinetics of omeprazole in humans have been described in some detail in recent years (14,15). The results of these studies indicate that omeprazole is rapidly and completely absorbed from the gastrointestinal tract when given in a sodium bicarbonate buffer to avoid gastric acid degradation. Because of its instability at low pH, omeprazole is administered as an enteric-coated formulation in clinical practice. The rate of absorption from this formulation is lower than from buffered solutions and suspensions originally used during drug development, while the bioavailability of the formulations, about 50%, is comparable (16). Omeprazole very rapidly distributes into a body space comparable to the volume of the extracellular water. The elimination of omeprazole, almost exclusively metabolic, is rapid, with a mean plasma clearance of about 650 ml/min and a terminal half-life of about 0.5 h. A major fraction, about 80%, of a given dose is recovered in the human urine as metabolites within 4 days and the remaining dose fraction is recovered in the feces. Recently, it was shown that biliary secretion accounts for the fecal recovery of intravenously administered omeprazole in humans (17). Impaired renal function has been shown to have no influence on omeprazole disposition (18,19).

The results from initial studies of the pharmacokinetic and pharmacodynamic properties of omeprazole have recently been reviewed (20,21). This paper focuses mainly on the interindividual variation in omeprazole absorption and on the disposition following oral and i.v. administration of a ^{14}C-labeled omeprazole dose.

MATERIALS AND METHODS

Drug Substance and Formulations

Radiolabeled [^{14}C]omeprazole (2-{[2-(3,5-dimethyl-4-methoxy)pyridylmethyl]sulfinyl}-5-methoxy-[2-^{14}C]benzimidazole (Fig. 1) and unlabeled omeprazole were dissolved in a mixture of polyethylene glycol (PEG) 400, water, and sodium bicarbonate (8 mmol) immediately before administration. The concentration of PEG 400 in the i.v. and oral doses was 40 and 4%, respectively. The total volumes were 10 and 50 ml, respectively. The

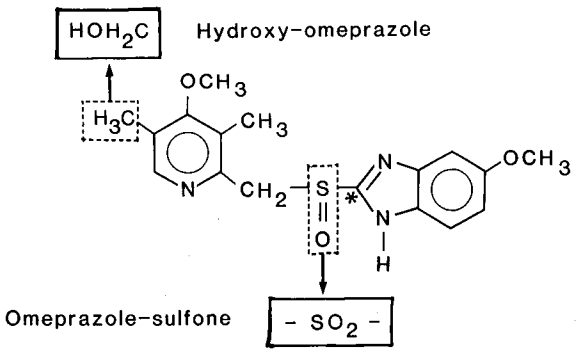

FIG. 1. Chemical structures of omeprazole and two of its major metabolites in the plasma. The asterisk indicates the position of the ^{14}C labeling.

specific radioactivity and concentration of the i.v. dose were 26.6 MBq/mmol (2.08 μCi/mg) and 1 mg of omeprazole/ml. The corresponding data of the oral dose were 13.4 MBq/mmol (1.05 μCi/mg) and 0.4 mg/ml. The radiochemical purity of [^{14}C]omeprazole was >97% as determined by high-performance liquid chromatography.

Study Design

Eight healthy males were recruited for the study. Their mean age was 27.1 ± 2.2 years and the mean weight was 74.1 ± 5.1 kg. All individuals had electrocardiograms, blood biochemistry, and hematological test values without clinically significant deviations. The subjects were informed both verbally and in writing about the experimental procedure and the purpose of the study and their written consent was obtained before the study was started. The protocol was approved by the Drug Department of the Swedish National Board of Health and Welfare, The Ethics Committee of the Medical Faculty of the University of Göteborg, and the Isotope Committee of the Sahlgren's Hospital, Göteborg.

The subjects were given 10 mg of omeprazole i.v. and 20 mg orally. The doses were administered in a randomized crossover design on two separate occasions with 1 to 4 weeks between study days. The i.v. dose was given by constant infusion of 2 mg/min over 5 min. A solution containing 16 mmol of $NaHCO_3$ in 100 ml of water was concomitantly given orally to mimic the sodium bicarbonate intake in association with the oral dose. The oral dose was followed by a solution of 50 ml of 0.16 mol/L $NaHCO_3$ that was used for rinsing of the vessel. In both the i.v. and oral experiment, 50 ml of 0.16 mol/L $NaHCO_3$ was administered 5 min before ad-

ministration and 10, 20, and 30 min postdosing. Each dose was taken after at least a 10-h fasting. Standardized meals were served after 2.5, 6, and 10 h.

Blood samples were drawn from an antecubital vein according to the following time schedule: 0, 3, 6, 10, 15, 20, 25, 35, 45, 55, 85, and 115 min and 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after dosing. For the i.v. dose, time 0 is identical to the ending of the infusion. During the first 12 h, an indwelling Venoject catheter was used. The catheter was kept open with a heparin lock. The samples were collected in heparinized tubes and cooled to room temperature, whereafter plasma was separated by centrifugation. The plasma was stored at −20°C until analyzed.

Urine was collected quantitatively during selected intervals (Fig. 6) over a 96-h period. Immediately after each collection, pH of the urine was adjusted to 7–8 with 1 mol/L Na_2CO_3. The urine was weighed and 10–15 ml stored at −20°C until analysis.

Feces was collected quantitatively each day over a 4-day period and samples were stored frozen until analysis.

Determination of Omeprazole and Two Metabolites in Plasma and Urine

The concentrations of omeprazole and two primary metabolites, omeprazolesulfone and hydroxyomeprazole, were determined in plasma and urine by liquid chromatography and UV detection according to previously described methods (22).

Determination of Total Radioactivity in Plasma, Urine, and Feces

Samples of plasma and urine (0.5 ml) were diluted with an equal volume of water and the total amount of radioactivity in the samples was determined by liquid scintillation counting after addition of 10 ml of scintillation cocktail.

Fecal samples were diluted with equal amounts of water and then homogenized. The homogenate (0.1 to 0.2 g) was treated at 80°C for 30 min with a mixture of 0.2 ml of concentrated perchloric acid and 0.2 ml of 30% hydrogen peroxide. After cooling to room temperature, 10 ml of scintillation cocktail was added followed by measurement of the radioactivity by liquid scintillation counting.

Calculations

A one-/two-compartment model was fitted to the postinfusion plasma concentrations of omeprazole after i.v. administration using the nonlinear least squares regression analysis program, NONLIN (23). The data were weighted by using their reciprocals, and the goodness of fit was evaluated according to the sum of squared deviations and the Akaike and Schwarz values.

The area under the plasma concentration–time curve (AUC) of i.v.-administered omeprazole was calculated from the slopes and intercepts of the fitted curve. The AUC after oral administration was calculated by the linear trapezoidal method for the ascending part of the curve and then by the log–linear method. Extrapolation to infinity was done by addition of C_t/λ_2, where C_t was the last measured plasma concentration and λ_2 was the elimination rate constant determined by log–linear regression of the terminal plasma concentration–time points.

Pharmacokinetic parameters were calculated as follows: (a) systemic clearance:

$$CL = \frac{D_{i.v.}}{AUC_{i.v.}}$$

(b) systemic availability:

$$f = \frac{AUC_{oral}}{AUC_{i.v.}} \cdot \frac{Dose_{i.v.}}{Dose_{oral}}$$

(c) volumes of distribution:

$$V_c = \frac{Dose_{i.v.}}{C_1 + C_2}$$

$$V_z = \frac{Dose_{i.v.}}{\lambda_z \, AUC_{i.v.}}$$

$$V_{ss} = \frac{Dose_{i.v.} \left(\frac{C_1}{\lambda_1^2} + \frac{C_2}{\lambda_2^2} \right)}{(AUC_{i.v.})^2}$$

where the C_i's and λ_i's are the intercepts and the rate constants, respectively, of the biexponential function describing the plasma concentration–time curve following transformation to a bolus dose (24).

The half-life of omeprazole after oral administration was determined from the individual regression lines of log plasma concentration vs. time in the postabsorptive phase.

The plasma concentrations of remaining metabo-

lites were calculated as the difference between the total concentration of radioactivity expressed as equivalents of omeprazole and the sum of the plasma concentrations of omeprazole, omeprazolesulfone, and hydroxyomeprazole.

Statistics

Student's t test for paired observations and the nonparametric Wilcoxon matched-pairs, signed-rank test were used to determine levels of significance.

RESULTS

Unchanged Drug

The plasma concentrations of omeprazole following both i.v. and oral dosing were substantially higher in two subjects (1 and 2) than in the other six (Tables 1 and 2). Consequently, median values and ranges, i.e., the concentrations in those individuals exhibiting the lowest (subject 7) and highest AUC (subject 2) of each dose, are presented in Fig. 2.

Following oral administration, the maximum concentration was attained within the first 0.5 h in all individuals. In five subjects, t_{max} was < 15 min. The median value for C_{max} was 1.2 μmol/L (range of 0.66 to 4.6 μmol/L) (Table 1). The systemically available fraction of the oral dose ranged between 25 and 117%, with a median of 38.7%. The individual absorption characteristics of omeprazole are listed in Table 1.

After the i.v. dose, the plasma concentration–time curve declined biphasically in each individual except in subject 6, in which the plasma levels decreased monoexponentially with time. Table 2 gives individual values of some disposition parameters associated with the two-compartment model.

TABLE 1. *Absorption characteristics of omeprazole calculated from a single oral dose of 20 mg (58 μmol) of the drug*

Subject no.	t_{max} (min)	C_{max} (μmol/L)	f
1	25	3.2	1.17
2	15	4.6	0.916
3	11	2.0	0.520
4	15	0.93	0.249
5	11	1.1	0.346
6	11	0.66	0.345
7	11	0.77	0.316
8	11	1.2	0.428
Median	11	1.2	0.387
Range	11–25	0.66–4.6	0.249–1.17

The half-life of the distribution phase, $t_{1/2\lambda 1}$, was very short and relatively consistent interindividually. The mean value was 3.0 ± 0.8 min. The drug was initially distributed into a mean body space (V_c) of 0.08 ± 0.03 L/kg. The mean volume of distribution at steady state (V_{ss}) was 0.24 ± 0.04 L/kg and the mean volume of distribution during the terminal phase (V_z) was 0.31 ± 0.09 L/kg.

The half-life of omeprazole in the terminal phase of the plasma concentration–time curve ($t_{1/2}$) was relatively short. Based on the intravenous plasma data, a median $t_{1/2}$ of 0.58 h (range of 0.27 to 2.52 h) was obtained (Table 2). Approximately the same value for the median $t_{1/2}$ was obtained for the oral dose while the range was 0.23 to 3.1 h (Table 3). The plasma clearance of omeprazole varied 14-fold between subjects (range of 59 to 828 ml/min) (Table 2). The median plasma clearance value was 624 ml/min.

Omeprazolesulfone

Omeprazolesulfone (Fig. 1) was present to a varying extent in plasma from all eight individuals. Figure 3 shows the plasma concentration–time profile for the oral dose constructed from median values and the corresponding curves in the two subjects having the lowest and highest concentrations of the omeprazolesulfone. The lowest concentrations of this primary metabolite were observed in the six subjects who rapidly eliminated the parent drug. In these subjects, the omeprazolesulfone concentration approached minimum determinable levels 3 to 5 h after oral dosing while high concentrations (600 to 750 nmol/L) of this metabolite were recorded in subjects 1 and 2 during this time period. The plasma levels of this metabolite normalized to the dose of the parent drug were 1.5 to 5 times higher after the oral dose than after i.v. administration in the six subjects who rapidly eliminated omeprazole. In subjects 1 and 2, however, the omeprazolesulfone plasma levels were twice as high after the oral 20 mg dose as after 10 mg i.v.

The half-life of the omeprazolesulfone was two to four times longer than that of omeprazole in all subjects (Table 3). There was a highly significant correlation between the half-life of the metabolite and the parent drug ($r = 0.99$; $p < 0.0005$). Figure 4 shows the plasma levels of these two compounds in subjects 1 and 2 over a 24-h period following the

TABLE 2. *Distribution characteristics of omeprazole calculated from the plasma levels following a single i.v. dose of 10 mg (29 μmol) of the drug*

Subject no.	V_c (L/kg)	V_{ss} (L/kg)	V_z (L/kg)	$t_{1/2\lambda 1}$ (min)		$t_{1/2}$ (h)	AUC (μmol h/L)	Cl (ml/min)
1	0.081	0.23	0.24	3.4		1.37	3.24	149
2	0.071	0.18	0.19	2.9		2.52	8.18	59
3	0.049	0.17	0.26	2.7		0.57	1.05	458
4	0.100	0.26	0.45	4.3		0.58	0.719	671
5	0.059	0.23	0.37	2.3		0.53	0.807	598
6[a]	0.26	0.26	0.26	—		0.27	0.584	826
7	0.14	0.30	0.43	3.5		0.41	0.583	828
8	0.052	0.26	0.30	2.1		0.69	0.743	649
Mean	0.079	0.236	0.313	3.03	Median	0.575	0.731	623.5
SD	± 0.034	± 0.042	± 0.093	± 0.82	Range	0.27–2.52	0.583–8.18	59–828

[a] Data compatible with the one-compartment model.

oral dose of omeprazole. The plasma concentrations of both compounds were below minimum determinable levels within 5 h after dosing in the remaining six subjects.

Hydroxyomeprazole

Hydroxyomeprazole was found in the plasma of all subjects studied. Furthermore, the results indicated also that the plasma levels of this metabolite were not normally distributed but could be grouped in the same way as for the parent drug and the omeprazolesulfone. However, the concentrations of hydroxyomeprazole were inversely related to the omeprazolesulfone concentrations so that subjects 1 and 2, with the highest plasma concentrations of the omeprazolesulfone, had very low concentrations of hydroxyomeprazole, while the remaining six subjects, who had a more rapid elimination of omeprazole, had high levels of hydroxyomeprazole in their plasma (Fig. 3 and Table 4).

Remaining Metabolites

The plasma concentrations of remaining metabolites showed essentially the same distribution pattern within the group of subjects studied as omeprazole and its two specifically determined metabolites. Figure 5 shows that the concentration of remaining metabolites was practically zero during the first 90 min after dosing in subject 2, while the median concentration already amounted to 1 μmol/L after 15 min.

Furthermore, no levels of these metabolites were observed in the plasma from subject 1 during the first 15 min. At later times, the concentration of remaining metabolites increased slowly and reached about the same levels as in the other sub-

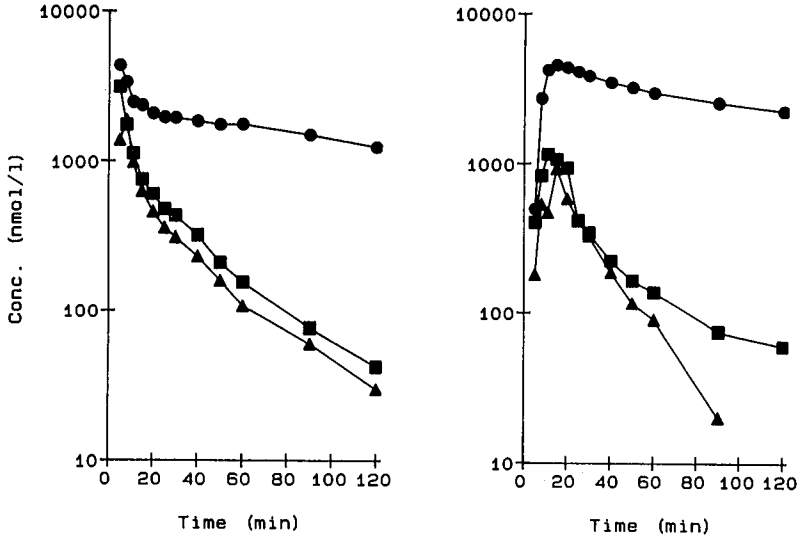

FIG. 2. Median (■), highest, and lowest individual plasma concentrations of omeprazole, following i.v. (**left**) and oral (**right**) administration of 10 and 20 mg of omeprazole, respectively: (●) subject 2, (▲) subject 7.

TABLE 3. *Elimination half-lives of omeprazole and the sulfone metabolite after oral administration of an acute 20 mg dose of omeprazole*

Subject no.	$t_{1/2}$ (h)	
	Omeprazole	Sulfone
1	2.1	7.5
2	3.1	11.0
3	0.67	1.2
4	0.23	0.95
5	0.70	2.0
6	0.35	0.75
7	0.32	0.90
8	0.63	1.3
Median	0.65	1.25
Range	0.23–3.1	0.75–11.0

The correlation coefficient (r) between the half-lives was 0.99; $p < 0.0005$.

jects 3 and 4 h after dosing. The AUCs of remaining metabolites from time 0 to 12 h after dosing are shown in Table 4.

Urinary Recoveries

The mean recoveries of the radioactive dose in the urine and feces over a period of 4 days after dosing are shown in Fig. 6. Almost complete recovery was achieved for both the i.v. (98.1 ± 2.9%) and oral dose (93.8 ± 4.0%) during this time period. In both cases, the major dose fraction was excreted by the kidneys. The mean urinary recovery was 78.3 ± 2.3% after the i.v. dose and 75.7 ± 2.6% for the oral dose. Negligible amounts, <0.1% of the administered dose, were recovered as unchanged omeprazole. A minor amount (<1.5% of the i.v. dose and <0.9% of the oral dose) was due to the omeprazole-sulfone, while the excretion of hydroxyomeprazole in the urine varied between 4.6 to 15.5% of a given dose during the first 12 h after oral administration (Table 5). Subjects 1 and 2 differed in their renal excretion of hydroxyomeprazole from the rest of the group. During the first 2 h after dosing, only 2.0 and 3.0% of hydroxyomeprazole were found in the urine from these two subjects. In subjects 3 to 8, the corresponding amounts ranged between 9.1 to 13.7% of a given omeprazole dose. The 2-h recovery of hydroxyomeprazole was only 38 to 43% of the amount of metabolite excreted during 12 h in subjects 1 and 2, while in subjects 3 to 8, the fractions were 78 to 88%. After the i.v. dose, the excreted amount of hydroxyomeprazole during each collection period was approximately halved in each individual. The renal excretion of remaining metabolites was very rapid. Within the first hour, 20 to 31% of a given i.v. radioactive dose was excreted as remaining metabolites in the urine from the six subjects who rapidly cleared the drug. The corresponding figures for subjects 1 and 2 were 8.2 and 4.5%, respectively. After 24 h, however, comparable fractions of given radioactivity, mainly remaining metabolites, were recovered in all eight subjects, with a range of 69.8 to 78.2%.

DISCUSSION

The results of the present study point to some interesting features of the pharmacokinetics of ome-

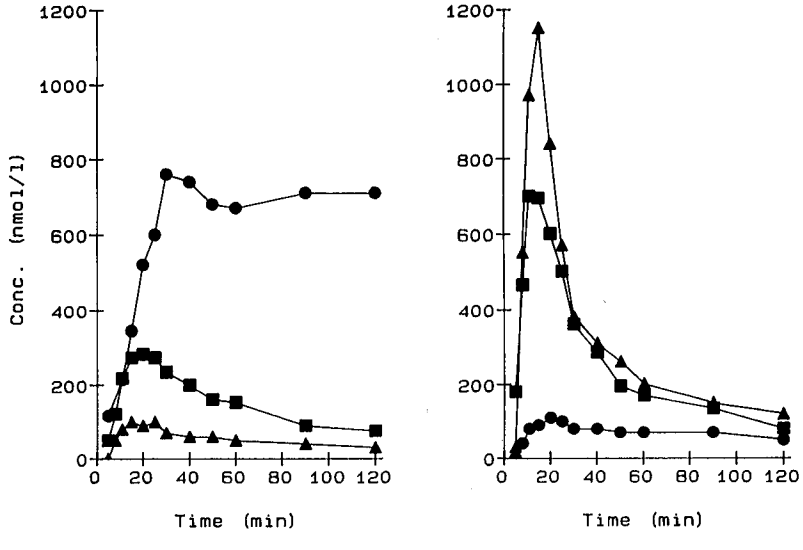

FIG. 3. Median (■), highest, and lowest individual plasma concentrations of omeprazole-sulfone (**left**) and hydroxyomeprazole (**right**) following oral administration of 20 mg of omeprazole: (●) subject 2, (▲) subject 8 for the sulfone, and subject 5 for hydroxyomeprazole.

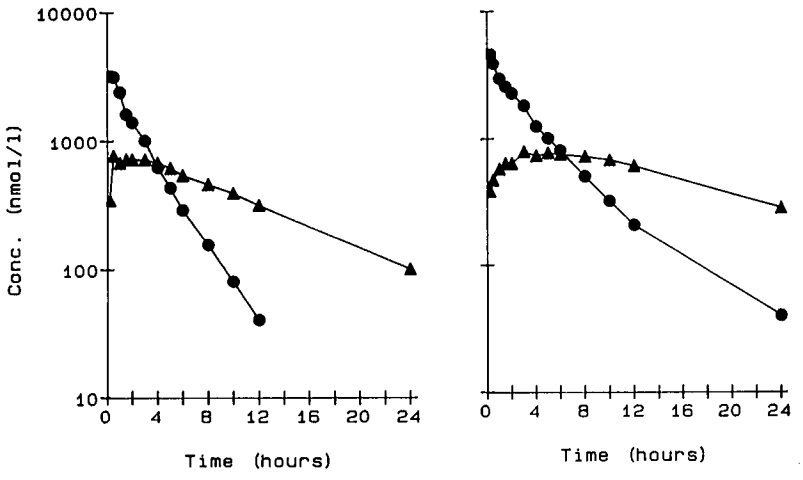

FIG. 4. Plasma concentrations of omeprazole (●) and omeprazolesulfone (▲) in subjects 1 (left) and 2 (right) following oral administration of 20 mg of omeprazole.

prazole. The drug is very rapidly absorbed from an alkaline solution, the peak occurring after 10 to 15 min in most individuals. Based on the median values for t_{max} and the terminal rate constant, the half-life for the absorption process was found to be about 4.5 min. Absorption already in the stomach or in the duodenum, in which case gastric emptying would be the rate-limiting step, might explain the very short time between dosing and the reaching of maximum plasma levels of omeprazole.

Following oral administration, two subjects (1 and 2) showed significantly higher concentrations of omeprazole than the rest of the subjects. This was due to a lower elimination rate and two to three times greater bioavailability of omeprazole in these two individuals than in the other six. Since the drug was very rapidly absorbed and the total urinary recoveries of the oral and i.v. dose were the same, the interindividual differences between the f values of omeprazole would unlikely be due to incomplete absorption from the gastrointestinal tract. Instead, the reason for the interindividual variation in f might be found in extensive first-pass metabolism in subjects 3 to 8. Another possibility might be that the intake of sodium bicarbonate was insufficient to prevent decomposition of omeprazole due to failure to neutralize the gastric acid in association with drug administration. Of these explanations, extensive first-pass elminiation seems to be the most probable one, since f was found to be highly correlated to systemic clearance ($r = -0.91$, $p < 0.0025$).

The individual values of the volume of distribution terms were normally distributed. The correlations between these terms and CL were, however, rather weak ($r = 0.68$ for V_β vs. CL and $r = 0.75$ for V_{ss} vs. CL, $p < 0.05$). The initially available body space is somewhat higher than the plasma volume and V_β has a value similar to that of the extracellular water. The small volume of distribution of ome-

TABLE 4. *Individual AUCs (μmol h/L) of omeprazole, two of its primary metabolites, the omeprazolesulfone and hydroxyomeprazole, and of the remaining metabolites*

Subject no.	Omeprazole AUC	Sulfone AUC	Hydroxyomeprazole $AUC_{0-3\ h}$	Remaining metabolites $AUC_{0-12\ h}$
1	7.6	9.8	0.24	2.9
2	15.0	17.7	0.19	0.80
3	1.1	0.93	0.69	3.7
4	0.36	0.37	0.56	3.4
5	0.50	0.53	0.69	3.6
6	0.40	0.34	0.48	4.8
7	0.37	0.37	0.58	3.6
8	0.67	0.19	0.50	3.4
Median	0.57	0.45	0.53	3.5
Range	0.36–15.7	0.19–17.7	0.19–0.69	0.8–4.8

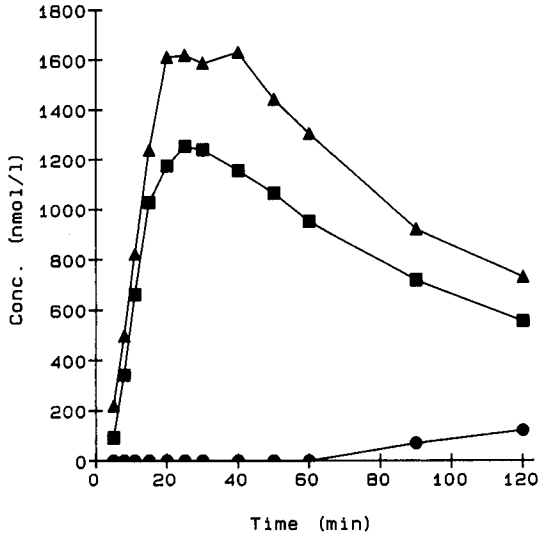

FIG. 5. Median (■), highest, and lowest individual plasma concentrations of the remaining metabolites following oral administration of 20 mg of omeprazole: (●) subject 2, (▲) subject 6.

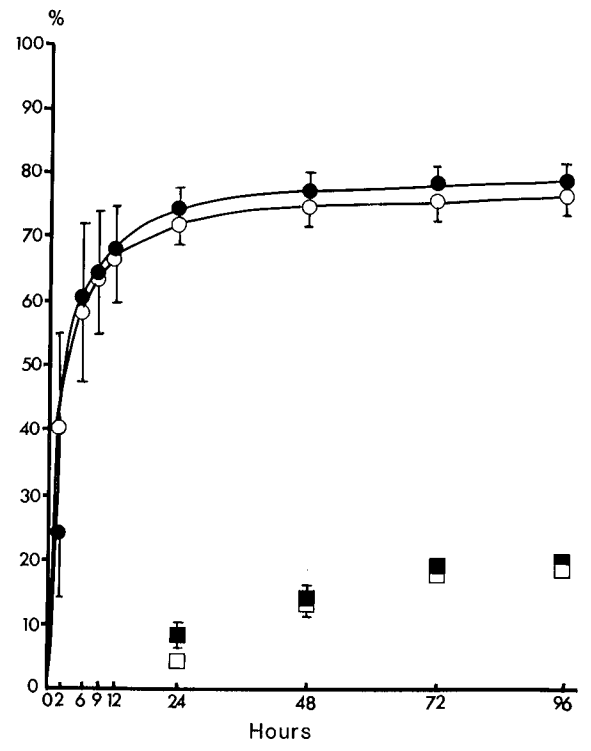

FIG. 6. Accumulated urinary (○) and fecal (□) recoveries of radioactive metabolites following i.v. (●, ■) and oral (○, □) administration of 10 and 20 mg of omeprazole, respectively. The bars indicate ±SD.

prazole indicates that about one-fifth of the total amount of omeprazole in the body was confined to the plasma at distribution equilibrium.

No attempt was made to determine the degree of protein binding or the distribution of the drug between plasma and erythrocytes in the present study. In a previous study, the binding to plasma proteins was about 95% and the ratio between the omeprazole concentration in whole blood and plasma was approximately 0.6 in human blood (20). This ratio results in a blood clearance that is on average 67% higher than plasma clearance, i.e., the median blood clearance was 1,040 ml/min in the present study.

There was a 14-fold intersubject variation in omeprazole clearance, with subjects 1 and 2 as distinct outliers, as regards their capacity to eliminate omeprazole. A similar variation was found for the terminal half-life, which increased with decreasing clearance capacity ($r = 0.89$, $p < 0.0025$). The low omeprazole clearance in subjects 1 and 2 was reflected in slower formation of hydroxyomeprazole and remaining metabolites compared to that of the other six subjects. The ability of the former subjects to oxidize omeprazole to the corresponding omeprazolesulfone, however, seemed to be comparable with that in the majority of the group. The effect of a reduced formation rate of hydroxyomeprazole and remaining metabolites was most pronounced in subject 2. The plasma from this subject contained high concentrations of omeprazolesulfone but very low concentrations of hydroxyomeprazole and undeterminable levels of remaining metabolites during the first 60 min after dosing. This was in clear contrast with the findings in subjects 3 to 8 in which the plasma levels of hydroxyomeprazole and remaining metabolites exceeded those of the parent drug and the omeprazolesulfone during the major part of the blood collection period. These results suggest that the hydroxylation of omeprazole and possibly some other metabolic reaction in the elimination of this drug is subjected to a genetic influence, as has been reported for several other drugs, e.g., debrisoquine,

TABLE 5. *Individual accumulated excretion of hydroxyomeprazole in the urine following oral administration of 20 mg (58 μmol) of omeprazole*

Time (h)	% of dose							
	#1	#2	#3	#4	#5	#6	#7	#8
1	1.1	1.8	6.8	6.0	11.4	7.6	7.7	9.3
2	2.0	3.0	9.9	11.2	13.7	9.1	9.3	10.2
4	3.1	4.8	12.0	12.6	15.0	10.2	10.1	11.2
6	3.8	6.1	12.5	13.1	15.3	10.5	10.4	11.5
9	4.4	7.2	12.5	13.8	15.4	10.6	10.4	11.6
12	4.6	7.8	12.7	14.1	15.5	10.6	10.5	11.6

some β-blockers, and mephenytoin (25,26). A debrisoquine test of subjects 1 and 2, however, showed that they were extensive metabolizers of this drug and therefore their capacity to metabolize omeprazole did not seem to be associated with debrisoquine hydroxylase deficiency.

The consistently longer half-life of omeprazolesulfone than that of the parent drug in all subjects studied suggests rate-limited elimination kinetics of omeprazolesulfone. Like the parent drug, omeprazolesulfone was eliminated at a much lower rate in subjects 1 and 2 than in the rest of the subjects studied. This was indicated by the high and sustained plasma levels of this metabolite and its much longer half-life in these two subjects. The highly significant correlation between the half-life of omeprazolesulfone and of omeprazole suggests also that the further metabolism of omeprazolesulfone is affected by the same genetic enzyme modification as the metabolism of omeprazole. This seems to be very reasonable if omeprazolesulfone is hydroxylated to an appreciable degree in the same position as omeprazole.

The half-life of omeprazole and of omeprazolesulfone showed the same deviation from normal distribution as systemic clearance and bioavailability. However, in spite of about a tenfold range between the extreme values, the half-life of omeprazole in subject 2, about 3 h, is too short to cause any accumulation of the drug with the recommended once-daily dosing regimen. For the pharmacologically inactive omeprazolesulfone with a longer half-life of about 11 h in subject 2, there will be an approximately 30% increase in the plasma levels from the first dose to steady state, which in practice already occurs after the second dose.

The concentration of remaining metabolites in plasma was probably to some extent due to the corresponding acid of hydroxyomeprazole. This acid has previously been identified and recovered in human urine in similar amounts as hydroxyomeprazole (27). Furthermore, since only negligible amounts of omeprazolesulfone were recovered in the urine, it seems reasonable to assume that a significant portion of the remaining metabolites was formed by oxidation of omeprazolesulfone to, for instance, the hydroxysulfone and its corresponding acid as mentioned above.

Negligible amounts of unchanged drug were recovered in the urine in all subjects irrespective of their capability to clear omeprazole. Similarly, the more polar omeprazolesulfone metabolite was only marginally excreted by the kidneys in all eight subjects. Accordingly, both the parent drug and omeprazolesulfone require further metabolism to probably more polar and less extensively plasma protein-bound compounds that then can be excreted in the urine. Because of this, renal elimination of omeprazole and its sulfone metabolite did not increase in subjects 1 and 2 despite their reduced capability to metabolize these two compounds. However, since formation of omeprazolesulfone seems to be the major primary metabolic process in the elimination of omeprazole in these two individuals, their urine will probably contain a greater fraction of metabolites originating from omeprazolesulfone than from other primary metabolites compared to the urine from the other six subjects.

Since omeprazole is acid-labile with a half-life of about 1.8 h at pH 6 and 37°C (28), the renal clearance of this compound might be underestimated due to degradation in acidic urine already in the bladder. However, this potential artefact was virtually avoided in this study since concomitant intake of sodium bicarbonate maintained the pH of the urine between 6 and 8 during the first 12 h after dosing. Since urine was collected hourly, while approximately 50% of the dose was excreted, the fraction of the excreted amount of omeprazole being degraded before collection was estimated to be less than 15%.

The observation that some individuals have a substantially higher AUC of omeprazole than the majority of subjects because of slower metabolism implies that by using a dose that is effective in virtually all patients, a small number of them will be given a dose that is higher than would be necessary from an effect point of view. However, extensive clinical studies have shown a practically 100% healing rate of acid-related disorders, with a very low incidence of side effects with doses of 20 or 40 mg once daily. Therefore, the potential adverse clinical implications of the interindividual variation in the amount of omeprazole reaching the systemic circulation are negligible. It should also be made clear that a half-life of about 3 h, which probably is close to a maximum value for omeprazole, is too short to cause accumulation during repeated administration with the recommended once-daily regimen.

In conclusion, this study has demonstrated a rather wide interindividual variation in the clearance of omeprazole that can be related to individuals' ability to form hydroxyomeprazole and possibly some other metabolite(s). Oxidation of omepra-

zole to the corresponding sulfone seems to be poorly correlated to the hydroxylation capacity while the further metabolism of omeprazolesulfone appears to be closely related to the individual's ability to form hydroxyomeprazole. Potentially, the observed interindividual variations in omeprazole and omeprazolesulfone disposition are genetically related but further studies are needed to obtain estimates of the range and frequency distribution of individual clearance values in the population. These findings are considered to have negligible clinical relevance.

REFERENCES

1. Larsson H, Carlsson E, Junggren U, et al. Inhibition of gastric acid secretion by omeprazole in the dog and rat. *Gastroenterology* 1983;85:900–7.
2. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin-stimulated acid secretion in man. *Gut* 1983; 24:270–6.
3. Lauritsen K, Rune SJ, Bytzer P, Kelback KH, Jensen KG. Effect of omeprazole and cimetidine on duodenal ulcer. *N Engl J Med* 1985;312:958–61.
4. Bardhan KD, Bianchi Porro G, Bose K, Hincliffe RFC, Lazzaroni M. Comparison of two different doses of omeprazole versus ranitidine in duodenal ulcer (DU) healing. *Gut* 1985;26:A557–8.
5. Classen M, Dammann HG, Domschke W, Hengels KJ, Hüttemann W. Kurzzeti-Therapie des Ulcus duodeni mit Omeprazole und Ranitidin. *Dtsch Med Wochenschr* 1985; 110:210–5.
6. Bate CM, Bradby CVH, Wilkinson SP, et al. Omeprazole provides faster ulcer healing and symptom relief than cimetidine in the treatment of gastric ulcer. *Gut* 1988;29:A1440–1.
7. Walan A, Bader J-P, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med* 1989;320:69–75.
8. Dehn TCB, Shepardh HA, Colin-Jones D, Kettlewell MGW. A double blind comparative study of omeprazole (40 mg od) versus cimetidin (400 mg qds) in the treatment of erosive reflux oesophagitis. *Gut* 1988;29:A1440.
9. Klinkenberg-Knol ED, Jansen JMBJ, Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicenter comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1987;1:349–51.
10. Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. Omerpazole in Zollinger–Ellison syndromes. *N Engl J Med* 1984;310:758–61.
11. McArthur KE, Collen MJ, Maton PN, Cherner JA, Howard J. Omeprazole; effective, convenient therapy for Zollinger–Ellison syndrome. *Gastroenterology* 1985;88:939–44.
12. Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^+K^+)-APTase. *Nature (Lond)* 1981;290:159–61.
13. Ganser AL, Forte JG. K^+-stimulated ATPase in purified microsomes of bullfrog oxyntic cells. *Biochim Biophys Acta* 1973;307:169–80.
14. Howden CW, Meredith PA, Forrest JAH, Reid JL. Oral pharmacokinetics of omeprazole. *Eur J Clin Pharmacol* 1984;26:641–3.
15. Regårdh CG. Pharmacokinetics and metabolism of omeprazole in man. *Scand J Gastroenterol* 1986;suppl 118:99–105.
16. Pilbrant Å, Cederberg C. Development of an oral formulation of omeprazole. In: Borg KO, Olbe L, eds. *Omeprazole. A survey of preclinical data.* Mölndal, Sweden: A.B. Hässle, 1985:113–20.
17. Lind T, Andersson T, Skånberg I, Olbe L. Biliary excretion of intravenous [^{14}C]omeprazole in humans. *Clin Pharmacol Ther* 1987;42:504–8.
18. Howden CW, Paytom CD, Meredith PA, MacDougall AL. Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. *Eur J Clin Pharmacol* 1985;28:637–40.
19. Naesdal J, Andersson T, Bodemar G, et al. Pharmacokinetics of [^{14}C]omeprazole in patients with impaired renal function. *Clin Pharmacol Ther* 1986;40:344–51.
20. Regårdh CG, Gabrielsson M, Hoffmann KJ, Löfberg I, Skånberg I. Pharmacokinetics and metabolism of omeprazole in animals and man—an overview. *Scand J Gastroenterol* 1985;suppl 108:79–94.
21. Clissold SP, Campoli-Richards DM. Omeprazole. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger–Ellison syndrome. *Drugs* 1986;32:15–47.
22. Lagerström P-O, Persson B-A. Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. *J Chromatogr* 1984;390:347–56.
23. Metzler CM, Elfring L, McEwen AJ. A user manual for NONLIN and associated programs. Research Biostatistics, The Upjohn Company, Kalamazoo, MI.
24. Loo JCK, Riegelman S. Assessments of pharmacokinetic constants from post infusion blood curves obtained after iv infusion. *J Pharm Sci* 1970;59:53–7.
25. McGourty JC, Silas JH, Lennard MS, Tucker GT, Woods HF. Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985;20:555–66.
26. Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol* 1984;26:753–9.
27. Renberg L, Simonsson R, Hoffman K-J. Identification of two main urinary metabolites of [^{14}C]omeprazole in man. *Drug Metab Disp* 1989;17:69–76.
28. Brändström A, Bergman N-Å, Lindberg P, et al. Chemical reactions of omeprazole and omeprazole analogues. II. Kinetics of the reaction of omeprazole in the presence of 2-mercaptoethanol. *Acta Chem Scand* 1989;43:549–68.