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# Pharmacokinetics and metabolism of omeprazole in animals and man - an overview

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The pharmacokinetics of omeprazole have been studied to varying extent in the mouse, rat, dog and in man.

The drug is rapidly absorbed in all these species. The systemic availability is relatively high in the dog and in man provided the drug is protected from acidic degradation in the stomach. In man the fraction of the oral dose reaching the systemic circulation was found to increase from an average of 40.3 to 58.2 % when the dose was raised from 10 to 40 mg, suggesting some dose-dependency in this parameter.

The drug distributes rapidly to extra-vascular sites. The volume of distribution,  $V_d$ , in man is comparable to the volume of the extracellular water. The penetration into the red cells is low, the ratio between the concentration in whole blood and in plasma being about 0.6. Omeprazole is bound to about 95 % to proteins in human plasma. The binding is lower in the dog and rat (90 and 87 %, respectively).

Omeprazole is eliminated almost completely by metabolism and no unchanged drug has been recovered in the urine in the species studied. Two metabolites, characterised as the sulfone and sulfide of omeprazole, have been identified and quantified in human plasma. The mean elimination half-life in man and in the dog is about 1 hour, whereas half-lives in the range of 5 to 15 minutes have been recorded in the mouse. In two studies in man, the mean total body clearance was 880 and 1097 ml  $\times$  min<sup>-1</sup>, indicating that omeprazole belongs to the group of high clearance drugs. In the dog, too, the drug appears to be rapidly cleared from the blood, the mean total body clearance being about 10.5 ml  $\times$  min<sup>-1</sup>  $\times$  kg<sup>-1</sup>.

In the rat and dog, 20 to 30 % of an i.v. or oral dose of omeprazole is excreted as metabolites in the urine and the remaining fraction is recovered in the faeces within three days after the administration. In man, the excretion of radioactivity via the kidneys is much more efficient and the recoveries in the excreta are approximately the reverse of those in the rat and dog.

*In vitro* studies with rat liver microsome preparations suggest that omeprazole and cimetidine inhibit cytochrome P-450-mediated metabolic reactions to about the same extent in equimolar concentrations. However, since the molar daily dose of cimetidine will be 25 to 50 times higher than that of omeprazole, the latter might have less influence on the mixed function oxidase system than cimetidine. Results obtained in man with antipyrine and aminopyrine support this hypothesis.

**Key-words:** Pharmacokinetics; disposition; metabolism; proteinbinding; drug interactions; animals; man

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## Introduction

Omeprazole, 5-methoxy -2-[(4-methoxy -3,5-dimethyl -2-pyridinyl) methyl] sulphonyl]H-

benzimidazole is a substituted benzimidazole which inhibits gastric acid secretion in animals and man. The drug acts via an interaction with H<sup>+</sup>K<sup>+</sup>ATPase – the gastric proton pump – in the

secretory membrane of the parietal cell (1). A single, oral dose of 20 to 80 mg omeprazole induces a dose-dependent and long-lasting inhibition of pentagastrin-stimulated gastric acid secretion in healthy volunteers (2, 3). The inhibitory effect on this parameters is further strengthened during the first days of repeated administration (2 - 4). Effect studies over 24 hours have revealed a profound decrease in intragastric acidity throughout the study period (5, 6).

When omeprazole has been given to duodenal ulcer patients, the recovery frequency has been extremely high. After four weeks of treatment, the healing rate has been over 90 % (7, 8). On the basis of these initial clinical studies omeprazole thus appears to be an effective drug in the treatment of duodenal ulcer. Its therapeutic potential is now being further assessed in comparative, clinical trials.

In this paper our present knowledge concerning the pharmacokinetics of omeprazole in various species is summarised.

## Animal pharmacokinetics

### Studies in the mouse

The plasma concentrations of omeprazole have been followed after oral administration of a single, oral dose of 40 and 400  $\mu\text{mol/kg}$  to groups of 5 starved, male mice, which were killed at various times after the administration. The doses were identical to the lowest and highest dose in the cancerogenicity study in this species and the same formulations were used. Omeprazole was analysed in plasma samples from each animal by liquid-solid chromatography and UV-detection (10).

Maximum plasma concentration was already recorded in the first sample drawn, i.e., 10 minutes after dosage, whereafter the concentration of omeprazole declined very rapidly to minimum detectable levels 0.5 and 2 hours after gavage. The mean maximum concentration increased from  $15.9 \pm 5.3 \mu\text{mol/l}$  after the lowest dose to  $155.4 \pm 24.5 \mu\text{mol/l}$  after the dose of 400  $\mu\text{mol/kg}$ , i.e., the concentration increased proportionally to the amount of drug administered. Estimated mean half-lives were in the range of 5 to 15 minutes with a tendency towards a longer half-life for the highest dose.

The distribution of omeprazole and its metabolites in the mouse has been studied by autoradiography and by liquid scintillation counting of various tissues (11).

### Studies in the rat

The absorption, excretion and tissue distribution of omeprazole have been studied in rats after intravenous and oral administrations of 10 and 100  $\mu\text{mol/kg}$ , respectively, to male, unstarved Sprague-Dawley rats. The doses contained trace amounts of  $^{14}\text{C}$ -labelled drug. The radiochemical purity was >99 % determined by liquid-solid chromatography.

Radioactivity measurements were performed according to the following procedures using Insta-Gel®, alternatively Dimilume®-30, as scintillation liquid. Faeces homogenates were combusted by a mixture of concentrated hydrogen peroxide (30 %) and perchloric acid (70 %) and blood was hemolysed in Soluene®-350/isopropanolol (1:1) and decolourised by hydrogen peroxide (30 %) prior to the addition of the scintillation liquid. Tissue homogenates were dissolved in 1 ml Soluene®-350. Counting was performed in a Mark III Model 6880 (Searle Analytical Inc.) liquid scintillation spectrometer. Quenching was corrected for by external standardisation.

### Recovery of the radioactive dose in urine and faeces

The urinary and fecal excretions of the radioactive i.v. and oral doses are given in Table I. After i.v. administration 25.9 % of the dose was excreted via the kidneys over a period of 72 hours, while the average cumulative urinary recovery of the oral dose during the same period was 22.7 %. In both experiments, more than 90 % of the total urinary recovery was excreted during the first 24 hours after dosage. The corresponding recoveries in the faeces over the entire collection period were 71.9 and 73.1 % of the i.v. and oral doses, respectively. Less than 0.1 % of the amount excreted via the kidneys was due to unchanged omeprazole.

These data indicate a complete gastrointestinal uptake of the radioactive oral dose, but further studies are needed for evaluation of the systemic availability of omeprazole in the rat.

Table I. The excretion of [ $^{14}\text{C}$ ] omeprazole and its total pool of metabolites after intravenous and oral administrations of 10  $\mu\text{mol/kg}$  and 100  $\mu\text{mol/kg}$ , respectively, to the rat. Mean values  $\pm$  SD from 4 rats.

Route of administration	Time (h)	Recovered radioactivity % of dose		
		Urine	Faeces	Total
i.v.	0 – 6	19.0 $\pm$ 1.0	0.6 $\pm$ 0.4	19.6 $\pm$ 1.8
	6 – 24	6.0 $\pm$ 1.4	68.0 $\pm$ 6.0	74.0 $\pm$ 3.9
	24 – 48	0.7 $\pm$ 0.1	2.8 $\pm$ 0.8	3.5 $\pm$ 0.8
	48 – 72	0.2 $\pm$ 0.1	0.5 $\pm$ 0.3	0.7 $\pm$ 0.4
	0 – 72	25.9 $\pm$ 2.0	71.9 $\pm$ 4.2	97.8 $\pm$ 4
p.o.	0 – 6	16.0 $\pm$ 1.9	0.2 $\pm$ 0.2	16.2 $\pm$ 1.9
	6 – 24	5.0 $\pm$ 0.4	48.2 $\pm$ 9.7	53.0 $\pm$ 9.5
	24 – 48	1.4 $\pm$ 0.6	20.8 $\pm$ 7.6	22.4 $\pm$ 7.6
	48 – 72	0.3 $\pm$ 0.1	3.9 $\pm$ 2.8	4.2 $\pm$ 2.8
	0 – 72	22.7 $\pm$ 1.5	73.1 $\pm$ 4.4	95.8 $\pm$ 2.3

### Tissue distribution of [ $^{14}\text{C}$ ]omeprazole and its metabolites

The concentrations of radiochemical entities have been determined in 15 different tissues of the rat at various times after i.v. and oral administrations of [ $^{14}\text{C}$ ]omeprazole. Table II shows the results for the i.v. dose. After 0.5 hours the highest concentrations, 12 to 23 nmol/g tissue, were found in the liver, kidneys and duodenum. The stomach and the

thyroid gland also contained comparatively high amounts of radioactivity. In all other tissues studied, the concentration of omeprazole plus metabolites was lower than in whole blood and plasma ( $\sim 3.5$  nmol/g). Particularly the brain contained low levels of radioactivity suggesting that omeprazole and/or its metabolites pass the blood brain barrier to a very limited extent. The high recovery of radioactivity in the stomach agrees with observations in the whole-body autoradiographic

Table II. Tissue distribution and retention of total radioactivity in the rat after intravenous administration of 10  $\mu\text{mol/kg}$  of [ $^{14}\text{C}$ ] omeprazole. Mean values  $\pm$  SD from 4 rats in nmol/g organ.

Tissue	Time after administration		Minimum detectable concentration
	0.5 h	72 h	
Blood	3.2 $\pm$ 1.0	0.79 $\pm$ 0.06	0.004
Plasma	3.6 $\pm$ 1.4	0.03 $\pm$ 0.02	0.002
Heart	1.9 $\pm$ 0.6	0.09 $\pm$ 0.01	0.04
Lungs	2.2 $\pm$ 0.6	0.12 $\pm$ 0.02	0.04
Liver	13.0 $\pm$ 4.0	0.34 $\pm$ 0.04	0.01
Kidneys	12.0 $\pm$ 4.0	0.28 $\pm$ 0.02	0.02
Brain	0.3 $\pm$ 0.1	<M.d.c.	0.03
Thymus	1.3 $\pm$ 0.8	<M.d.c.	0.09
Salivary glands	1.8 $\pm$ 0.6	<M.d.c.	0.1
Thyroid	5.2 $\pm$ 0.8	0.30 $\pm$ 0.12	0.07
Stomach	8.6 $\pm$ 3.0	0.09 $\pm$ 0.2	0.04
Duodenum	23.0 $\pm$ 6.0	<M.d.c.	0.2
Spleen	2.2 $\pm$ 0.2	0.19 $\pm$ 0.04	0.06
Fat (white)	0.6 $\pm$ 0.2	<M.d.c.	0.07
Muscle	1.3 $\pm$ 0.4	0.03 $\pm$ 0.02	0.02
Mean weight of 4 rats (g)	250	270	

M.c.d. = minimum detectable concentration

study of the mouse in which it was found that omeprazole was concentrated in the mucosal cells of the stomach (11).

Secretion into the bile or directly over the intestinal epithelium probably accounts for the high duodenal content of radioactivity after the i.v. dose. Insignificant amounts of unchanged omeprazole were recovered in the bile in a subsequent study, suggesting that the radioactivity in the duodenum of the rat is primarily due to metabolites. About 75 % of the given i.v. radioactive dose was recovered in the faeces over a period of 72 hours.

The distribution pattern of the oral dose was very similar to that of the i.v. dose though, as a consequence of the route of administration, the stomach and duodenum contained the highest amount of radioactivity during the first 6 hours following the administration.

The levels of unchanged omeprazole in the plasma 0.5 hours after the i.v. and oral dose were 9 and 6 % of the total radioactivity, respectively. Six hours after the administration the proportion of unchanged drug in the plasma had further decreased about tenfold.

## Studies in the dog

The pharmacokinetics of omeprazole have been studied in the dog to varying extents in several studies.

### Design of Study I

In the initial study (12) three dogs with gastric-duodenal fistulas were given 0.25  $\mu\text{mol/kg}$  i.v. via the vena antibrachii or intraduodenally via a duodenal fistula. Another three dogs provided with a Heidenhain pouch received 1.0  $\mu\text{mol/kg}$  by a stomach tube. Gastric acid secretion was induced in all dogs by continuous subcutaneous infusion of histamine, 150 to 400 nmol/kg/h, throughout the experiment. The dogs were deprived of food and water for about 18 hours prior to the start of the experiment.

The i.v. dose, dissolved in 40 % PEG 400 and 4 mM bicarbonate buffer (pH = 8), was given over a period of 1 to 2 minutes. The oral and intraduodenal doses were suspended in 0.5 % of a

Methocel®-water solution (0.5 %). Each dose contained a tracer dose of [ $^{14}\text{C}$ ]omeprazole.

Omeprazole was determined in plasma according to the method of Persson et al (10).

## Results and discussion

The mean plasma concentration-time curves of all three doses are shown in Figure 1. Following the i.v. dose the omeprazole plasma levels declined bi-exponentially in each dog. The average half-life of the terminal phase ( $t_{1/2\beta}$ ) was 62 minutes and the average volume of distribution,  $V_{\beta}$ , was 0.56 l/kg, i.e., about half of the actual body space. Total plasma clearance, determined by the ratio between the dose and the integrated area under the plasma concentration-time-curve (AUC) was 6.3  $\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$ . Since the ratio between the blood and plasma concentration of omeprazole is 0.60 in the dog (Table VII), the total body clearance of omeprazole in the dog would be about 10.5  $\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$ .

The intraduodenal dose of omeprazole was very rapidly absorbed. Maximum concentration was already attained during the first 5 to 15 minutes post dosage. The fraction of this dose available to

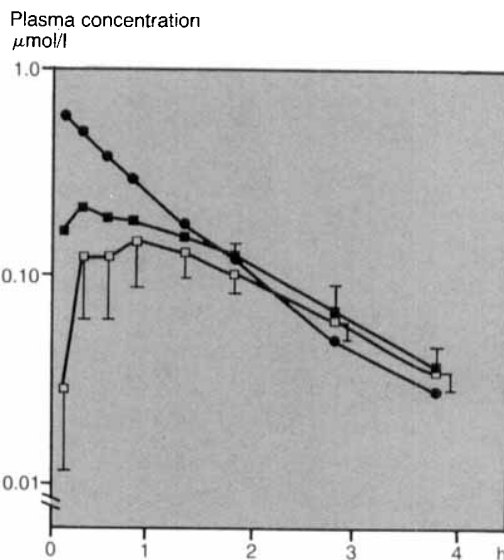


Figure 1. Plasma concentrations of [ $^{14}\text{C}$ ] omeprazole given i.v. (0.25  $\mu\text{mol/kg}$ ,  $n = 2$ ,  $\bullet$ ) or i.d. (0.25  $\mu\text{mol/kg}$ ,  $n = 3$ ,  $\blacksquare$ ) in the gastric fistula dog and orally (1  $\mu\text{mol/kg}$ ,  $n = 3$ ,  $\square$ ) in the Heidenhain pouch dog. Mean  $\pm$  SEM.

the systemic circulation was, on average, about 70 % determined by AUC comparisons. The mean half-life in the terminal phase of the plasma concentration-time-curve was essentially the same as for the i.v. dose, i.e., approximately one hour. Compared with the intraduodenal dose, intragastric administration resulted in a lower rate of absorption and a reduction in the systemic availability. Maximum concentration was obtained from 30 to 75 minutes after administration and the AUC was only about 15 % of that of a correspond-

ing i.v. dose of omeprazole. The terminal half-life was again close to one hour. The difference between the fraction of the intraduodenal and intragastric dose available to the systemic circulation is probably a consequence of acidic degradation of omeprazole in the histamine-stimulated stomach.

The average plasma concentration-time profiles of the total pool of radioactive metabolites following all three doses are shown in Figure 2. The radioactivity due to the metabolites declined essentially

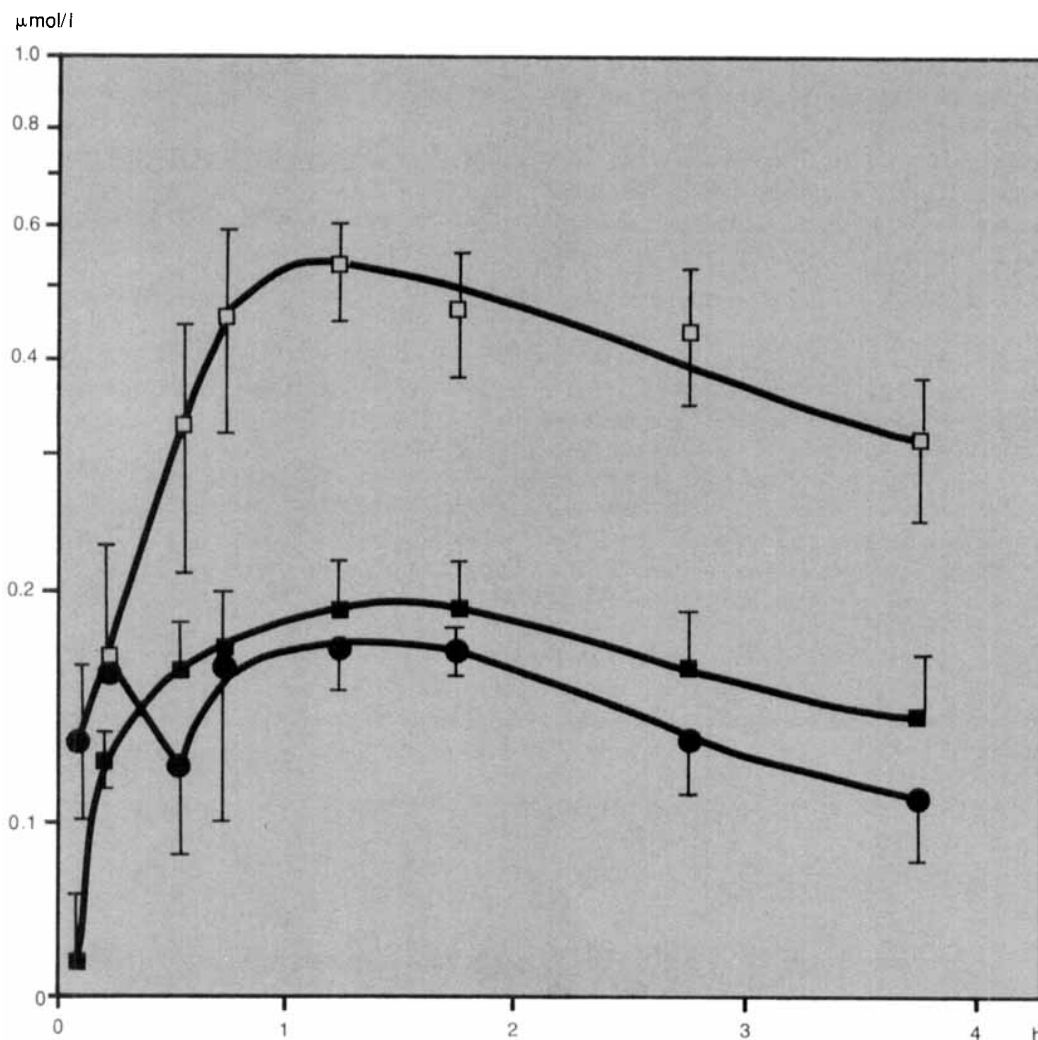


Figure 2. Plasma concentrations of radioactive metabolites following administration of [ $^{14}\text{C}$ ] omeprazole i.v. (0.25  $\mu\text{mol/kg}$ ,  $n = 2$ ,  $\bullet$ ) or i.d. 0.25  $\mu\text{mol/kg}$ ,  $n = 3$ ,  $\blacksquare$ ) in the gastric fistula dog and orally (1  $\mu\text{mol/kg}$ ,  $n = 3$ ,  $\square$ ) in the Heidenhan pouch dog. Mean  $\pm$  SEM.

mono-exponentially in each dog during the last two hours of each experiment. Estimated half-lives during this period were unrelated to the route of administration and ranged between 2.7 to 5.0 hours, i.e., in the dog some metabolite(s) is/are eliminated at a lower rate than that of the parent drug.

## Design of Study II

This study was performed to measure the excretion of [ $^{14}\text{C}$ ]omeprazole and its metabolites in the urine and faeces, following i.v. and oral administration of 0.25 and 1.0  $\mu\text{mol/kg}$ , respectively, to three dogs. The doses were given cross-over at least two weeks apart. The dogs had fasted for 18 hours prior to drug administration. Food and water were accessible 6 hours post dosage. The oral dose was given by an intragastric tube and the animals were kept in metabolic cages permitting separate collection of urine and faeces over a 72 hour period. The concentration of [ $^{14}\text{C}$ ]omeprazole and its radioactive metabolites was determined by methods previously described in the rat study.

## Results and comments

Totally, 87 % of the i.v. and 95 % of the oral dose were recovered in the excreta over a three-day period, Table III. During this time 32 % of the i.v. dose was excreted in the urine. The corresponding recovery of the oral dose was 21 %. The major fraction recovered in urine and faeces was excreted during the first 24 hours after the administration. During this period more than 80 % of the 72-hour

urinary recovery of both doses was excreted in the urine. Approximately 2/3 of the three-day fecal recovery was expelled with the faeces during the first 24 hours after both i.v. and oral administration.

In both experiments, the excretion of unchanged [ $^{14}\text{C}$ ]omeprazole in the urine was less than 0.5 %. No attempt was made to quantify unchanged drug in the faeces. However, preliminary analysis of bile from three bile-fistulated dogs has not revealed any unchanged omeprazole in the bile. Accordingly, omeprazole seems to be eliminated primarily by biotransformation in the dog. The metabolites are excreted rapidly via the kidneys, in the bile and/or over the gastrointestinal epithelium.

## Human pharmacokinetics

Two basic pharmacokinetic studies and one interaction study with aminopyrine and antipyrine have been completed in man until now.

## Balance study with single i.v. and oral [ $^{14}\text{C}$ ]omeprazole

### Study design

The absorption and disposition of i.v. and orally administered omeprazole have been studied in a single-dose study with 10 mg i.v. and 20 mg orally (13). The radioactive dose was 20  $\mu\text{Ci}$  of  $^{14}\text{C}$ -labelled omeprazole. The doses were administered

Table III. Excretion of [ $^{14}\text{C}$ ] omeprazole and its radioactive metabolites in the dog following i.v. and oral administration of 0.25 and 1.0  $\mu\text{mol/kg}$ , respectively, of  $^{14}\text{C}$ -labelled drug. (Mean  $\pm$  SD; n = 3).

Dose	Time h	Per cent of dose		
		Urine	Faeces	Total
i.v.	0-24	29.5 $\pm$ 0.7	38.2 $\pm$ 21.1	67.7 $\pm$ 21.8
	24-48	2.0 $\pm$ 0.9	15.2 $\pm$ 12.6	17.1 $\pm$ 12.7
	48-72	0.5 $\pm$ 0.1	1.4 $\pm$ 0.7	1.9 $\pm$ 0.8
	0-72	32.0 $\pm$ 1.1	54.7 $\pm$ 7.9	86.7 $\pm$ 8.3
oral	0-24	17.5 $\pm$ 6.4	51.9 $\pm$ 21.6	69.4 $\pm$ 24.2
	24-48	3.2 $\pm$ 3.2	16.0 $\pm$ 9.6	19.2 $\pm$ 12.2
	48-72	0.5 $\pm$ 0.3	5.7 $\pm$ 4.9	6.1 $\pm$ 5.1
	0-72	21.2 $\pm$ 3.5	73.6 $\pm$ 12.3	94.7 $\pm$ 13.3

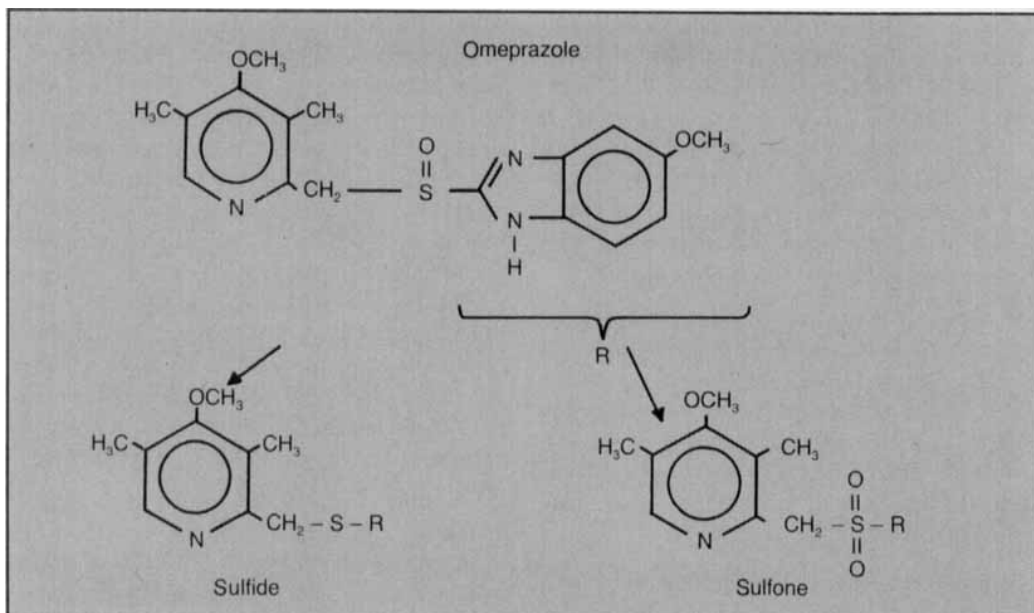


Figure 3. Chemical structure of omeprazole and two metabolites identified in human plasma.

randomised cross-over 1 to 4 weeks apart to eight, healthy, male volunteers, 24 to 31 years of age. Both doses were administered dissolved in a mixture of PEG 400 and water. The subjects were pre-treated with 8 mmol NaHCO<sub>3</sub> 5 minutes prior to drug administration. Sixteen mmol of bicarbonate were given together with each dose and during the next 30 minutes they received a further 8 mmol of bicarbonate every tenth minute to prevent degradation of the oral dose by the acid in the stomach.

[<sup>14</sup>C]omeprazole and the total pool of radioactive metabolites were measured in the plasma over 24-hours according to methods mentioned previously. In addition, two identified metabolites with the code-numbers H 168/22 and H 168/66, Figure 3, were quantified in the plasma over the same period of time. The identification of these two metabolites is described below.

Urine and faeces were collected quantitatively over a period of 96 hours and analysed for unchanged drug and metabolites according to previously described methods. The urine portions were adjusted to pH 7 to 8 by 1 M NaHCO<sub>3</sub> to prevent acidic degradation of omeprazole while waiting for analysis.

## Identification of omeprazole and two metabolites in human plasma

Pooled plasma samples from the individuals participating in the study were extracted with methylene chloride at pH 7.4. Aliquots of the organic phase were injected repeatedly onto a straight-phase LC column using 3.5 % methanol in methylene chloride as the mobile phase (10). The methanol contained 5 % of a solution of 25 % NH<sub>3</sub>. Fractions of the eluate with retention times identical to those of the references omeprazole, oxidised omeprazole (H 168/66, "omeprazole sulfone") and reduced omeprazole (H 168/22, "omeprazole sulfide") were collected. The "omeprazole sulfide" fraction was further purified using 2 % methanol in methylene chloride as mobile phase. The methanol contained the same proportion of NH<sub>3</sub> as in the first mobile phase. Collected fractions were evaporated to dryness and the residue was dissolved in 25 µl of methanol. The samples were then introduced into the mass spectrometer (MAT 112, Bremen. W Germany) by a direct inlet system. The sample rod was heated according to the following temperature programme:



ambient temperature for 10 seconds, 150°C for 35 seconds and flush evaporation to 300°C for 75 seconds. The sample rod was cooled to 30°C before the next analysis. The measurement was performed in repetitive scanning or selected ion monitoring mode. Identical retention times on the LC column and the presence of significant ions in the mass spectra of isolated plasma metabolite and synthesised reference were taken as identity.

The electron impact mass spectra of the isolated fractions of the human plasma having identical retention times to those of synthesised omeprazole and H 168/66 are given in Figure 4. These spectra were in all details identical to those of the two reference compounds confirming the existence of unchanged omeprazole, and "omeprazole sulfone" in human plasma.

The concentration of the metabolite with the same retention time as "omeprazole sulfide" was too low in the plasma to yield a complete mass spectrum like the one of the reference compound in Figure 5. Therefore, three characteristic ions; the molecular ion  $m/z 329^+$ , and  $(M-32)^+$ , and  $(M-32-15)^+$ , were used to improve the sensitivity of the mass spectrometer by selected ion monitoring. A fragmentation with the expected relative intensity of the three ions was obtained (Figure 5). The time for direct probe evaporation was the same for the metabolite as for the reference compound. According to these results, "omeprazole sulfide" can be assigned as a minor human plasma metabolite of omeprazole.

## Results and comments

The mean plasma concentration-time-curves following the i.v. and oral doses of omeprazole are shown in Figure 6. The oral solution of omeprazole was very rapidly absorbed. The average time of peaking,  $t_{max}$ , was 13.8 minutes (range 11 to 25 minutes). The maximum concentration varied seven-fold from 660–4580 nmol/l (mean 1914 nmol/l) and the mean systemic availability was 53.6 % (range 24.9 to 117.0 %).

The plasma levels of the i.v. dose declined bi-exponentially with time in all eight subjects and gave excellent fits to the equation of the two-compartment model on non-linear regression analysis. The mean half-life of omeprazole in the

initial, rapidly declining distribution phase,  $t_{1/2 \alpha}$ , was 3.0 min (range 2.1 to 4.3 min). The drug was initially distributed into a very limited fraction of the available body space. The average volume initially available for the distribution of omeprazole was 0.079 l/kg (range 0.052 to 0.139 l/kg, i.e., comparable with the blood volume. Also the apparent volume of distribution at pseudo-distribution equilibrium,  $V_{\beta}$ , was relatively small. The mean value was 0.31 l/kg (range 0.19 to 0.45 l/kg, which would be compatible with localisation of a major fraction of omeprazole in the extracellular water. The ratio between the blood volume and  $V_{\beta}$  suggests that about 25 % of the total amount of omeprazole in the body is confined to the blood.

Omeprazole was eliminated rapidly in all eight individuals. The average half-life was about 60 minutes (range 16 to 151 minutes). The total plasma clearance varied between 59 to 828  $ml \times min^{-1}$  (mean value 530  $ml \times min^{-1}$ ). Since the average ratio between the omeprazole concentration in blood and plasma is about 0.6 in man (see below), the average total blood clearance of omeprazole was about 880  $ml \times min^{-1}$  in this study.

The rapid elimination of omeprazole appears to be primarily due to metabolic processes since insignificant amounts of unchanged drug were excreted via the kidneys and in the stools. On the average, 78.2 % of the i.v. radioactive dose (range 74.3 to 81.9 %) was recovered in the urine over the collection period of four days. The corresponding recovery of the oral dose was 75.7 % (range 72.7 to 78.6 %). During the same period the fecal excretion was 19.3 % (range 15.0 to 24.3 %) for the i.v. dose and 18.3 % (range 13.6 to 20.7 %) after oral administration. The excretion of radioactive metabolites via the kidneys was initially very rapid and during the first six hours post dosage an average of about 60 % of the administered radioactive dose was recovered in the urine after both i.v. and oral omeprazole.

Only a minor fraction – less than 1 % – of the dose was excreted via the kidneys as the metabolite H 168/66. In spite of its low urinary recovery the metabolite H 168/66 was, however, available in the plasma in relatively high concentration, suggesting that this metabolite is either further metabolised before excretion via the kidneys or mainly

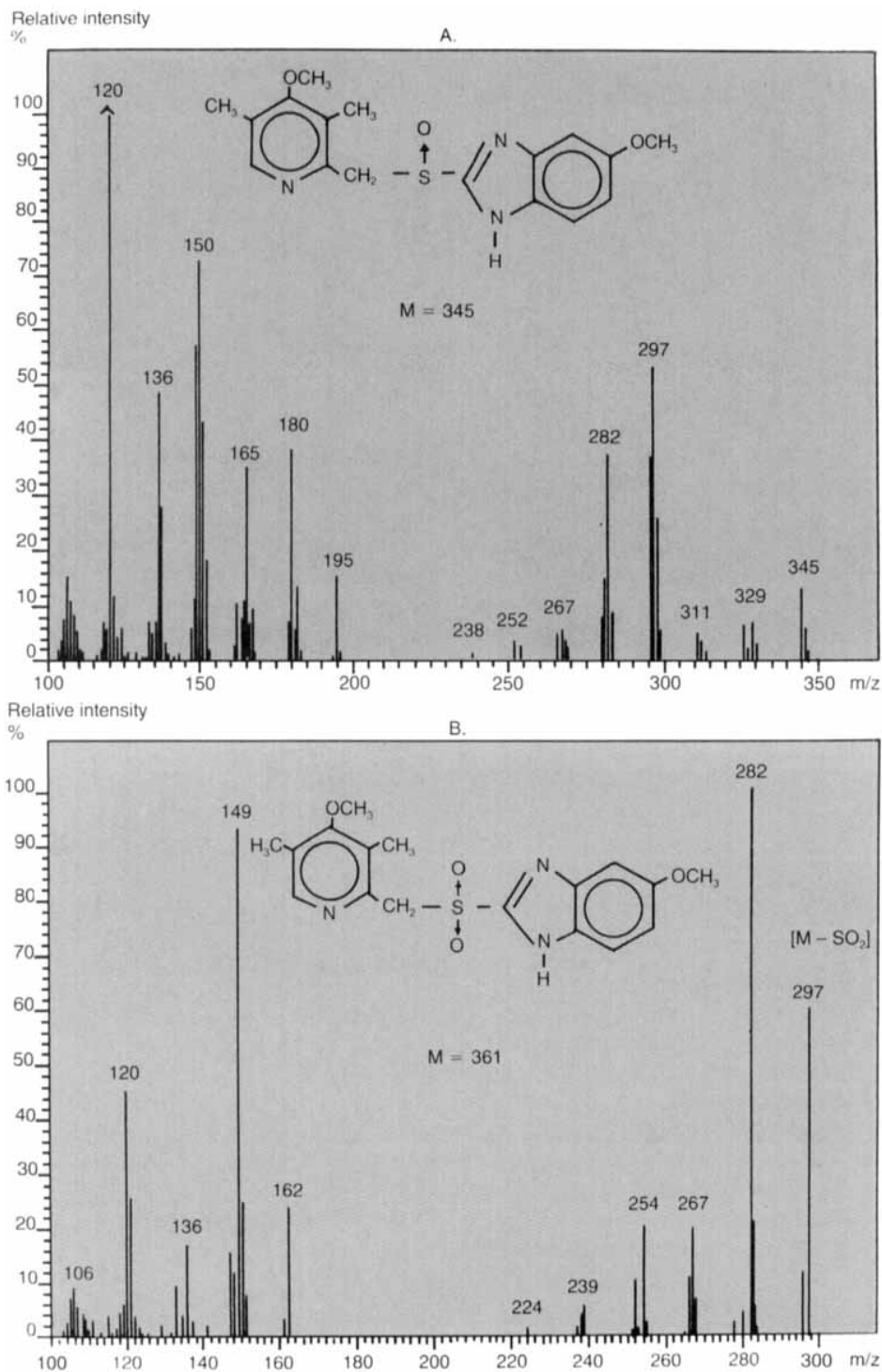


Figure 4. Electron impact mass spectrum of omeprazole (A) and metabolite H 168/66 (B) isolated from human plasma.

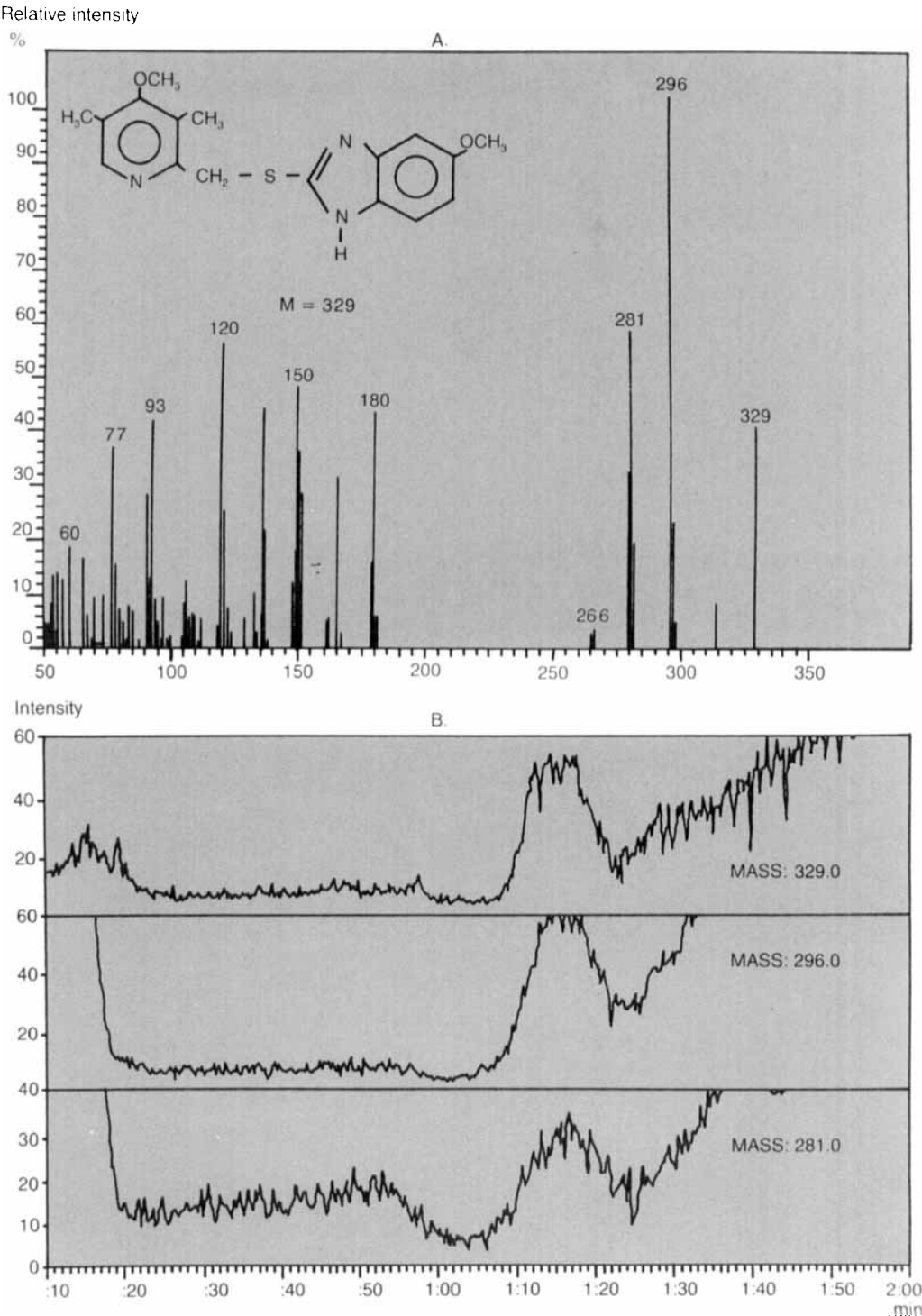


Figure 5. Electron impact mass spectrum of reference compound H 168/22 (A) and selected ion monitoring of plasma metabolite H 168/22 (B).

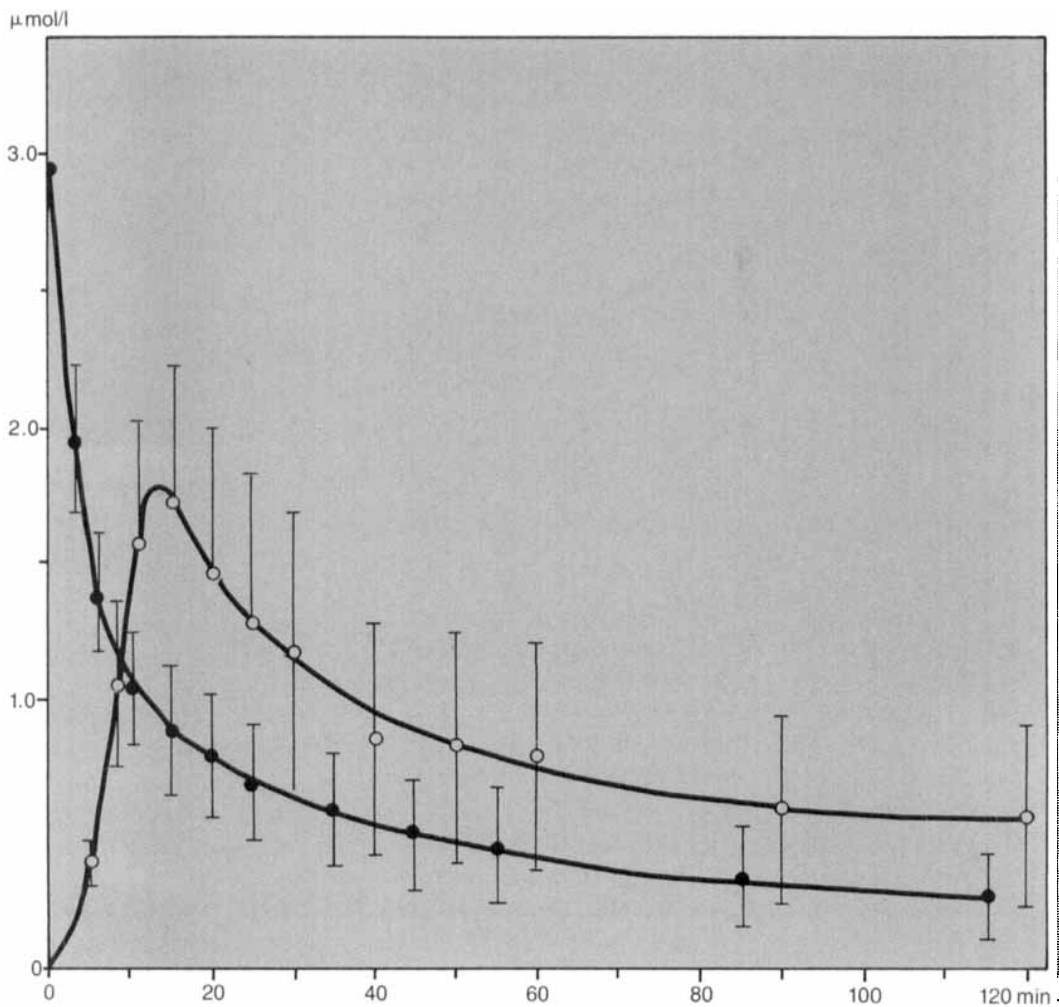


Figure 6. Mean plasma concentrations of omeprazole following administration of single doses of 10 mg (28.95  $\mu\text{mol}$ ) i.v. (●) and 20 mg (57.90  $\mu\text{mol}$ ) orally (○) to 8 young healthy subjects. The bars indicate SEM.

eliminated in the bile or by secretion over the gastrointestinal wall. Figure 7 shows the mean concentrations of omeprazole, H 168/66, and unidentified metabolites in the plasma over the first 2 hours following the i.v. dose of omeprazole. During this interval the concentrations of H 168/22 were consistently below minimum determinable levels ( $\sim 30 \text{ nmol/l}$ ).

## Effect of dose on the pharmacokinetics of omeprazole

### Study design

The effect of various i.v. and oral doses on the

kinetics of omeprazole has been evaluated in ten healthy, male subjects 19 to 27 (mean = 25) years of age (14). The subjects were given 10 and 40 mg omeprazole i.v. and 10, 40 and 90 mg orally randomised and cross-over. The drug was administered dissolved in a mixture of PEG 400 and water, and the buffer intake in association with the administration was the same as in the previous study.

### Results and comments

The mean plasma concentration-time-curves of omeprazole following the oral doses are given in Figure 8. The maximum concentration and AUC

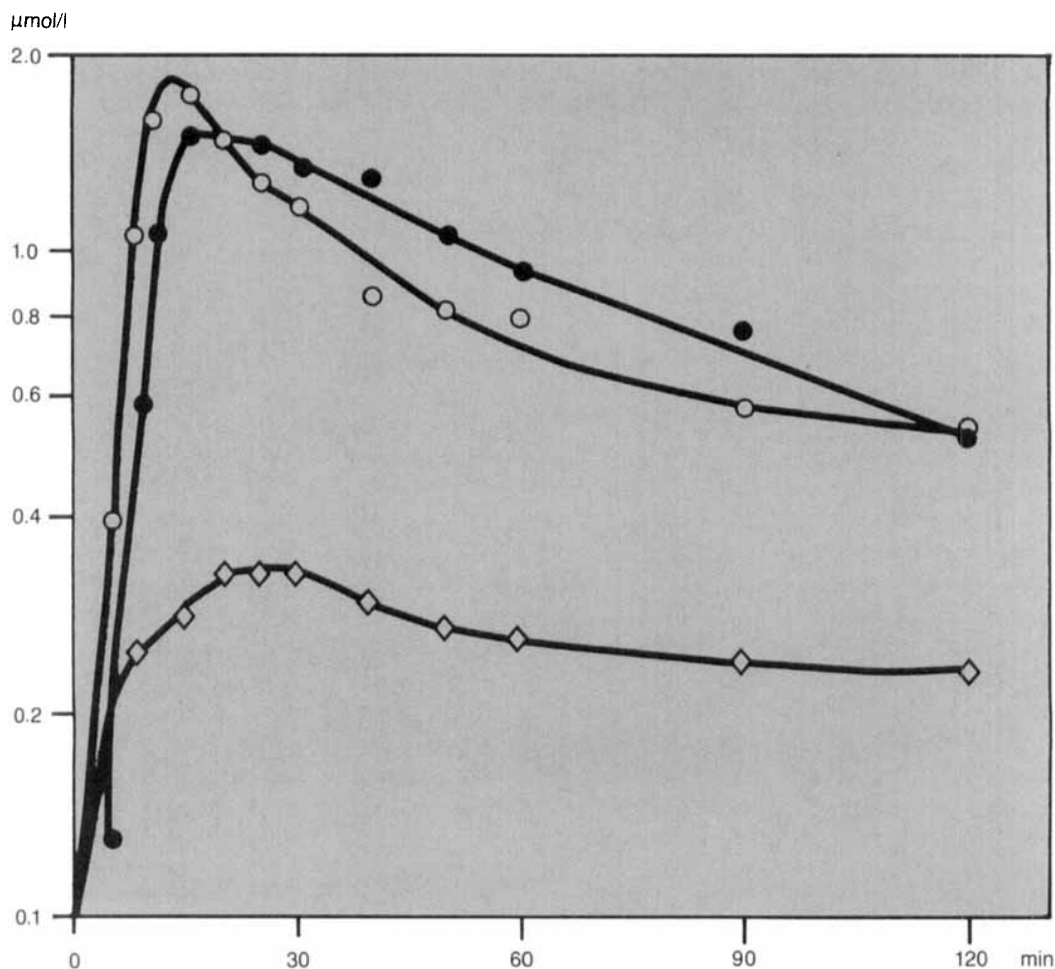


Figure 7. Mean plasma levels of omeprazole and its metabolites following a single oral dose of 20 mg omeprazole (omeprazole (n = 8) (○) omeprazole; (◇) H 168/66; (●) unidentified metabolites.

increased disproportionately with the amount of drug administered, resulting in dose-dependent systemic availability. On average, 40.3 % (range 14.9 to 73.4 %) of the oral 10 mg dose was available to the systemic circulation, while the value of this parameter increased to 58.2 % (range 29.0 to 105.0 %) for the 40 mg dose and further to 96.9 % (range 57.5 to 155.0 %) when 90 mg omeprazole was given orally.

The increase in systemic availability by 44 %, when the oral omeprazole dose was raised from 10 to 40 mg, appears to be caused primarily by a partial saturation of the first-pass effect since the mean plasma clearance of the corresponding i.v. doses

was unaffected by the dose (658 and 633 ml  $\times$  min<sup>-1</sup>). On the other hand, the further increase in F to a mean value of almost 100 % for the oral 90 mg dose probably resulted from a continued saturation of the first-pass effect in combination with reduced systemic clearance. F-values in the range of 140 to 160 % in three individuals and a significant increase in the mean  $t_{1/2}$  from 29 minutes for the 40 mg dose to 45 minutes after 90 mg orally support this hypothesis. However, since this high dose was not given i.v., adjustments for potentially altered systemic clearance of the 90 mg dose in relation to the 10 and 40 mg i.v. dose could not be made in the calculations of F of the highest oral dose.

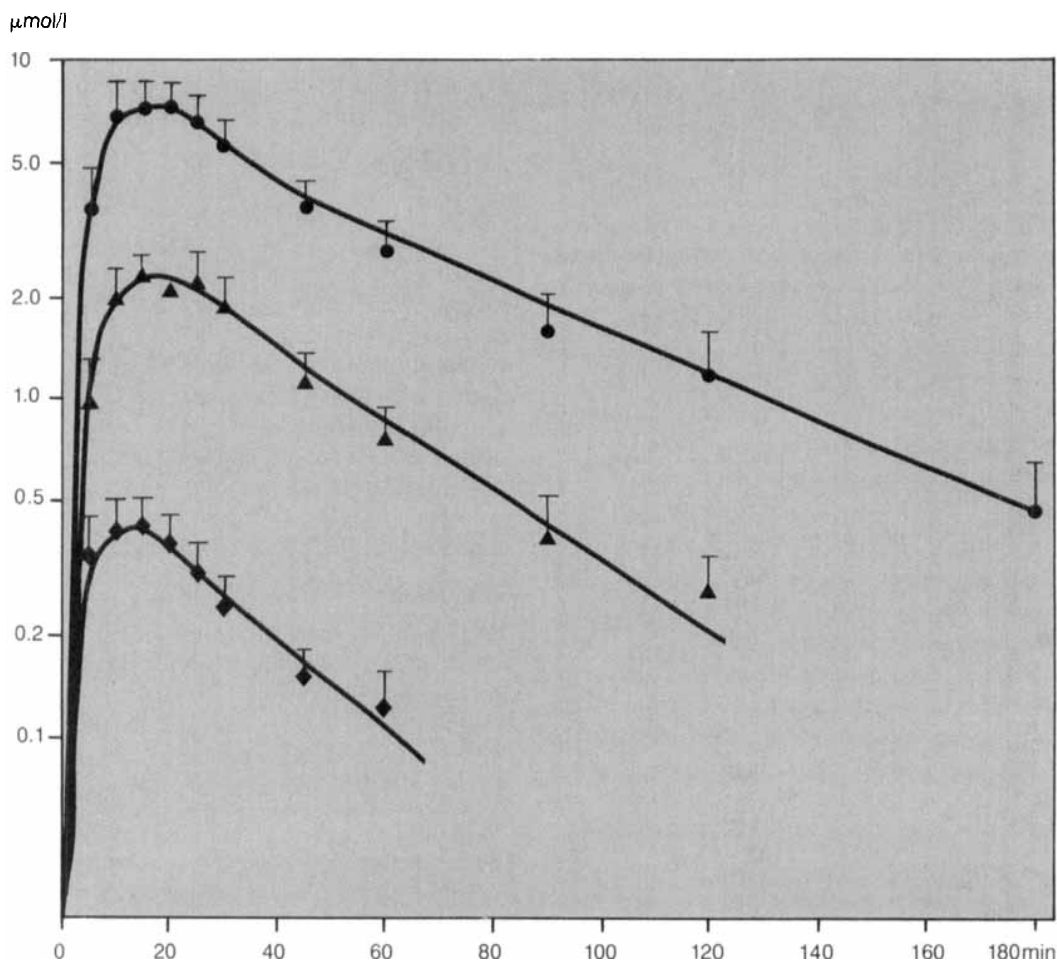


Figure 8. Mean plasma levels of omeprazole following administration of 3 single oral doses of omeprazole ( $n = 10$ ). The bars indicate SEM.

(◆) 10 mg (28.95  $\mu\text{mol}$ )  
 (▲) 40 mg (115.8  $\mu\text{mol}$ )  
 (●) 90 mg (260.6  $\mu\text{mol}$ )

Some disposition characteristic of the two i.v. doses derived according to the two-compartment model are presented in Table IV. Calculated parameters were in good agreement with those derived from the

i.v. dose of [ $^{14}\text{C}$ ]omeprazole. There was no indication of any dose-related changes in these parameters when the i.v. dose was increased from 10 to 40 mg.

Table IV. Some disposition characteristics of omeprazole in man determined from an i.v. dose of 10 mg and 40 mg, respectively (Mean  $\pm$  SD;  $n = 10$ ).

Dose	$V_c$ $\text{l} \cdot \text{kg}^{-1}$	$V_\beta$ $\text{l} \cdot \text{kg}^{-1}$	$t_{1/2\beta}$ h	Plasma clearance $\text{ml} \cdot \text{min}^{-1}$
10 mg i.v.	$0.14 \pm 0.03$	$0.34 \pm 0.04$	$0.48 \pm 0.04$	$658 \pm 37$
40 mg i.v.	$0.15 \pm 0.02$	$0.37 \pm 0.05$	$0.59 \pm 0.08$	$633 \pm 42$

Binding to plasma proteins

The binding of omeprazole to rat, dog, and human plasma proteins, human serum albumin (HSA) and  $\alpha_1$ -acid glucoprotein ( $\alpha_1$ -AGP) has been studied at ambient temperature and at 37 °C by the ultrafiltration technique (15).

Omeprazole in concentrations covering the normal range of therapeutic i.v. and oral doses was added to fresh plasma, solutions of HSA (Albumin, Kabi; purity >95 %;  $6.8 \times 10^{-4}$  M) an  $\alpha_1$ -AGP (Sigma;  $0.8 \text{ mg} \times \text{ml}^{-1}$ ) in phosphate buffer pH = 7.35, I = 0.167. Trace amounts of [ $^3\text{H}$ ]omeprazole (radiochemical purity 98.4 %) were added to each sample, and the concentration of omeprazole in the plastic bag and in the ultra-filtrate was determined by liquid scintillation counting.

Omeprazole was bound to about 95.5 % in the human plasma at 20 °C, Table V. The degree of binding was not affected by a hundred-fold variation in the concentration. The binding was less extensive in the dog and the rat, in which the average binding was close to 90 and 87 %, respectively, Table V. Like in the human plasma, the degree of binding was constant in the plasma of these animal species over the concentration interval studied.

Table V. Binding of omeprazole to human, dog, and rat plasma at 20 °C. (Mean  $\pm$  SD)

Plasma conc $\mu\text{mol} \cdot \text{l}^{-1}$	Per cent bound omeprazole		
	Man	Dog	Rat
0.19	95.8 $\pm$ 0.42 (n = 7)	90.3 $\pm$ 0.61 (n = 4)	87.5 <sup>a</sup>
1.9	95.7 $\pm$ 0.40 (n = 7)	89.3 $\pm$ 0.94 (n = 4)	87.0 <sup>a</sup>
19.4	95.5 $\pm$ 0.17 (n = 3)		

a = plasma pooled from 7 rats

Table VI. Binding of omeprazole to HSA and  $\alpha_1$ -acid glucoprotein. (Mean  $\pm$  SD; n = 4)

Concentration omeprazole $\mu\text{M}$	Per cent bound					
	HSA 20 °C	HSA 37 °C	$\alpha_1$ -AGP 20 °C	$\alpha_1$ -AGP 37 °C	HSA + $\alpha_1$ -AGP 20 °C	HSA + $\alpha_1$ -AGP 37 °C
0.2	94.0 $\pm$ 0.10	92.4 $\pm$ 0.02	87.8 $\pm$ 1.15	86.3 $\pm$ 0.88	95.6 $\pm$ 0.05	93.4 $\pm$ 0.17
2.0	93.8 $\pm$ 0.24	91.9 $\pm$ 0.24	74.4 $\pm$ 0.95	76.1 $\pm$ 0.31	95.5 $\pm$ 0.03	93.7 $\pm$ 0.17

The binding of omeprazole to isolated and purified HSA and  $\alpha_1$ -AGP in physiological concentrations is given in Table VI. The average binding to HSA was 93.8 % at 20 °C, i.e., about 2 % lower than in human plasma. An increase in the temperature from 20 to 37 °C reduced the binding to HSA by about 2 % (p < 0.05). Omeprazole was less extensively bound to  $\alpha_1$ -AGP and the binding to this protein seemed to be saturable at high concentrations, while the binding was essentially unaffected by a change in temperature from 20 to 37 °C. When HSA and the glucoprotein were mixed in physiological concentrations, the binding of omeprazole at 20 °C was virtually identical to that in human plasma, suggesting that the drug is primarily bound to these plasma protein fractions.

Ratio between blood and plasma concentration

Omeprazole has ampholytic properties. The acid dissociation constants are  $10^{-4.4}$  and  $10^{-8.8}$ . The drug therefore exists mainly in neutral form in the blood and only about 4 % is ionised. The partition coefficient of the neutral molecule between octanol and water is 240 (M Erickson, personal communication).

The ratio between the concentration of omeprazole in whole blood and plasma has been studied *in vitro* by incubating blood from the mouse, rat and dog, as well as man, with 40  $\mu\text{mol/l}$  of omeprazole over a period of 2 and 30 minutes. With the exception of the rat, ratios of about 0.6 were recorded after both 2 and 30 minutes of incubation, Table VII. Assuming a hematocrite value of 0.45, these results suggest that omeprazole distributes into red cells to a low extent, the ratio between the concentration in the erythrocytes and plasma being approximately 0.1. This ratio appears initially to be about twice as high in the rat.

Table VII. The ratio between the blood and plasma concentrations of total radioactivity after incubation of [ $^{14}\text{C}$ ] omeprazole (40  $\mu\text{mol/l}$ ; 8 Mbq/l) in blood samples from different species at a temperature of 37°C.

Time	Mouse	Rat	Dog	Man
2'	0.62	0.66	0.60	0.59
30'	0.63	0.78	0.60	0.62

The *in vivo* distribution of omeprazole between human erythrocytes and plasma has been studied in 6 healthy individuals 20 and 60 minutes after oral administration of a buffered solution of 20 mg omeprazole. The individual ratio between the drug concentration in whole blood and in plasma at identical sampling times are given in Table VIII. The mean ratios of 0.59 and 0.58 10 and 60 minutes after dosage were virtually identical to the partition coefficients in the *in vitro* experiments although the concentrations were 20 to 200 times lower in the *in vivo* study.

## Interactions with other drugs

### Animal studies

The effect of omeprazole on the microsomal metabolism of various model substrates has been studied *in vivo* and in rat liver preparations (16).

Omeprazole and cimetidine inhibited the metabolism of ethoxycoumarine and aminopyrine to

Table VIII. The ratio between the concentration of omeprazole in blood (B) and plasma (P) 10 and 60 min after oral administration of a solution of 20 mg omeprazole.

Subject	B/P	
	10 min	60 min
1	0.65	0.51
2	0.59	0.61
3	0.50	0.62
4	0.61	0.57
5	0.56	0.57
6	0.60	0.60
M	0.585	0.580
SD	$\pm 0.051$	$\pm 0.040$

Table IX. Concentrations ( $I_{50}$ ) of omeprazole and cimetidine causing 50 % inhibition of rat liver microsomal catalyzed degradation of various substrates.

Drug	$I_{50}$		
	Ethoxy-coumarine	Amino pyrine	p-nitro-anisole
Omeprazole	0.8	0.5	0.9
Cimetidine	0.9	0.6	6.0

about the same extent in equimolar concentrations, while omeprazole inhibited the O-demethylation of p-nitroanisole more effectively than cimetidine, Table IX.

Omeprazole had a moderate effect on hexobarbital sleeping time and aminopyrine half-life, following oral administration of 20 or 400  $\mu\text{mol/kg}$  to the rat. The mean sleeping time increased from 14.5 minutes in the control experiment to 18.3 minutes ( $p < 0.05$ ) after the high omeprazole dose, and  $t_{1/2}$  of aminopyrine increased from 24.5 minutes in the control animals to 37.1 minutes after a single dose of 400  $\mu\text{mol/kg}$  omeprazole. Repeated administration o.d. with this dose had no further effect on the aminopyrine half-life.

The moderate effect of omeprazole on the elimination rate of hexobarbital and aminopyrine contrasted clearly with the effect of an i.p. dose of 320  $\mu\text{mol/kg}$  of cimetidine. The histamine  $\text{H}_2$ -receptor blocker increased the average hexobarbital sleeping time by a factor of 9, and the mean  $t_{1/2}$  of aminopyrine was 87.6 min, i.e., more than twice that during omeprazole treatment.

### Study in man

The effect of omeprazole on oxidative drug metabolism has been studied in man using the model drugs antipyrine and [ $^{14}\text{C}$ ]aminopyrine (17). Analyses were made of the antipyrine half-life, clearance rates and aminopyrine  $^{14}\text{CO}_2$  half-life before and at the end of a 14-day treatment period with 30 or 60 mg of omeprazole each morning. The two omeprazole doses had no significant effect on the aminopyrine half-life or the metabolic clearance rate of antipyrine, while the half-life of antipyrine was increased by, on average, 10 % ( $p < 0.025$ ) after the 60 mg dose of omeprazole. The lower dose had no influence on this parameter.



## References

1. Wallmark B, Jaresten B-M, Larsson H, Rydberg B, Brändström A, Fellenius E. Differentiation among inhibitory actions of omeprazole, cimetidine, and  $\text{SCN}^-$  on gastric acid secretion. *Am J Physiol* 1983;245:G64-71.
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. Howden CW, Reid JL, Forrest JAH. Effect of omeprazole on gastric acid secretion in human volunteers. *Gut* 1983;24:A498.
4. Müller P, Dammann H-G, Seitz H, Simon B. Effect of repeated, once daily, oral omeprazole on gastric secretion. *Lancet* 1983;1:66.
5. Walt RP, Gomes M, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24-hour intragastric acidity. *Br Med J* 1983;287:12-4.
6. Prichard PJ, Yeomans ND, Mihaly G, Brian Jones D, Smallwood RA, Louis WJ. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983;287:1378-9.
7. Gustavsson S, Lööf L, Adami H-O, Nyberg A, Nyrén O. Rapid healing of duodenal ulcers with omeprazole; double blind dose-comparative trial. *Lancet* 1983;2:124-5.
8. Walan A, Bergsäter-Aspöy J, Farup P, Gillberg R, Halvorsen L, Kilander A, Lind T, Naesdal J, Of-fergaard S. Four week study of the rate of duodenal ulcer healing with omeprazole. *Gut* 1983;24:A972.
9. Daly MJ, Howe AL, Misiewicz JJ, et al. Omeprazole in duodenal ulcer disease: tolerance, acid inhibition, and endoscopic healing. *Br Med J* 1984;289:525-8.
10. Persson B-A, Lagerström P-O, Grundevik I. Determination of omeprazole and metabolites in plasma and urine. *Scand J Gastroenterol* 1985;20(suppl 108):71-7.
11. Helander H, Ramsay C-H, Regårdh C-G. Localization of omeprazole and metabolites in the mouse. *Scand J Gastroenterol* 1985;20(suppl 108):95-104.
12. Larsson H, Carlsson E, Junggren U, Olbe L, Sjöstrand SE, Skånberg I, Sundell G. Inhibition of gastric acid secretion by omeprazole in the dog and rat. *Gastroenterology*. 1983;85:900-7.
13. Regårdh CG, Lundborg P, Ekenved G, Heggelund A, Lagerström P-O, Reinhold A. Pharmacokinetics of omeprazole: Single dose study following intravenous and oral administration. To be published.
14. Skånberg I, Cederberg C, Lagerström P-O, Lundborg P, Nyberg G, Regårdh CG. Omeprazole pharmacokinetics in healthy subjects treated with single intravenous and oral doses. To be published.
15. Lunde PKM, Rane A, Yaffe SJ, Lund L, Sjöqvist F. Plasma protein binding of diphenylhydantoin in man. *Clin Pharmacol Ther* 1970;11:846-55.
16. Skånberg I, Holmström M. The effect of omeprazole on in vitro and in vivo microsomal drug metabolism in the rat. To be published.
17. Henry DA, Sommerville KW, Kitchingman G, Langman M. Omeprazole: effects on oxidative drug metabolism. *Br J Clin Pharmacol*. 1984;18:195-200.