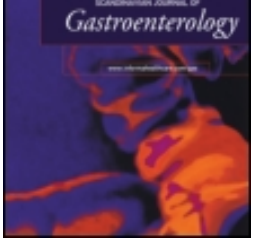

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Pharmacokinetics and metabolism of omeprazole in animals and man - an overview

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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_β, 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^{-1}, 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^{-1} $\times$ kg^{-1}.

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] sulphinyl]1H-benzimidazole is a substituted benzimidazole which inhibits gastric acid secretion in animals and man. The drug acts via an interaction with H^+K^+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 extremly 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 μmol/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 ± 5.3 μmol/l after the lowest dose to 155.4 ± 24.5 μmol/l after the dose of 400 μmol/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 μmol/kg, respectively, to male, unstarved Sprague-Dawley rats. The doses contained trace amounts of ^{14}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/isopropranolol (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}C] omeprazole and its total pool of metabolites after intravenous and oral administrations of 10 μmol/kg and 100 μmol/kg, respectively, to the rat. Mean values ± SD from 4 rats.

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

Tissue distribution of [^{14}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}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 (~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 μmol/kg of [^{14}] omeprazole. Mean values ± SD from 4 rats in nmol/g organ.

Tissue	Time after administration		Minimum detectable concentration
	0.5 h	72 h	
Blood	3.2±1.0	0.79±0.06	0.004
Plasma	3.6±1.4	0.03±0.02	0.002
Heart	1.9±0.6	0.09±0.01	0.04
Lungs	2.2±0.6	0.12±0.02	0.04
Liver	13.0±4.0	0.34±0.04	0.01
Kidneys	12.0±4.0	0.28±0.02	0.02
Brain	0.3±0.1	<M.d.c.	0.03
Thymus	1.3±0.8	<M.d.c.	0.09
Salivary glands	1.8±0.6	<M.d.c.	0.1
Thyroid	5.2±0.8	0.30±0.12	0.07
Stomach	8.6±3.0	0.09±0.2	0.04
Duodenum	23.0±6.0	<M.d.c.	0.2
Spleen	2.2±0.2	0.19±0.04	0.06
Fat (white)	0.6±0.2	<M.d.c.	0.07
Muscle	1.3±0.4	0.03±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 μmol/kg i.v. via the vena antibrachi or intraduodenally via a duodenal fistula. Another three dogs provided with a Heidenhain pouch received 1.0 μmol/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}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_β, 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 $ml \times min^{-1}kg^{-1}$. 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 $ml \times min^{-1}kg^{-1}$.

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

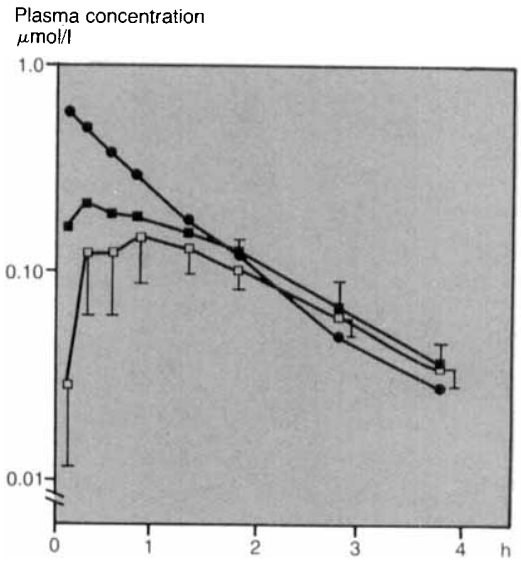

Figure 1. Plasma concentrations of [^{14}C] omeprazole given i.v. (0.25 μmol/kg, n = 2, ●) or i.d. (0.25 μmol/kg, n = 3, ■) in the gastric fistula dog and orally (1 μmol/kg, n = 3, □) in the Heidenhahn pouch dog. Mean±SEM.

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