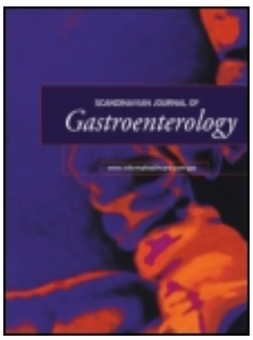

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C G Regårdh

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Pharmacokinetics and Metabolism of Omeprazole in Man

CG REGÅRDH
Department of Pharmacokinetics and Drug Metabolism, AB Hässle, Mölndal, Sweden

Four studies of the pharmacokinetics and metabolism of omeprazole are briefly discussed. Two of these were carried out in young healthy subjects and indicated that about 54% of an oral dose is available to the systemic circulation. The distribution of omeprazole after an intravenous dose was consistent with localization of a major fraction of the drug in the extracellular water, with about 25% restricted to the blood. Omeprazole was rapidly cleared and possessed the characteristics of a high clearance drug; insignificant amounts of ^{14}C-omeprazole were excreted by the kidneys, though metabolites were excreted very rapidly. Six different metabolites were reported, the major one being hydroxy-omeprazole. Increasing the intravenous dose of omeprazole from 10 mg to 40 mg had no significant effect on the pharmacokinetic parameters determined. A study in patients with impaired renal function showed that this had little effect on the kinetics of omeprazole, though excretion of metabolites was significantly affected. A study of elderly healthy subjects suggested that the disposition characteristics of omeprazole are affected to some extent by age; further studies are needed to elucidate the clinical implications. Omeprazole has been reported to prolong the half-life of diazepam which may be due to inhibition of the demethylation of diazepam. The interaction of omeprazole with the kinetics of aminopyrine and antipyrine was much less pronounced.

CG Regårdh, Department of Pharmacokinetics and Drug Metabolism, AB Hässle, S-431 83 Mölndal, Sweden

Omeprazole 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 omeprazole, 20–80 mg, induces a dose dependent and long-lasting inhibition of pentagastrin stimulated gastric acid secretion in healthy volunteers (2, 3). The inhibitory effect is further strengthened during the early days of repeated administration (2–4). Inhibition studies over 24 hours have revealed a profound decrease in intragastric acidity throughout the study period (5, 6).

In this presentation, results from four different studies on the pharmacokinetics and metabolism of omeprazole in man will be discussed briefly. Two of these studies were carried out in young, healthy subjects and cover the first single dose study with ^{14}C-labelled omeprazole (balance study) and potential dose dependency in the therapeutic dose range. The third study deals with omeprazole kinetics in patients with varying degrees of renal impairment and the fourth was performed in healthy, elderly individuals. Results of some drug interaction studies with omeprazole are also discussed briefly.

METHODS

A general outline of the studies is given below. Between 8 and 12 subjects were included in each study group. Cold (unlabelled) omeprazole was given intravenously, 10 or 20 mg, or orally, 20 or 40 mg. Radioactively labelled (^{14}C) omeprazole was administered in doses of 20 μCi (740 kBq). The variables recorded in the different studies were plasma levels of omeprazole and of identified metabolites, total plasma pool of metabolites, and urinary excretion of total pool of metabolites.

In the dose dependency study, single doses of

omeprazole, 10 or 40 mg i.v., or 10, 40 or 90 mg p.o., were given. The oral doses of omeprazole were administered as buffered solutions while the intravenous doses were dissolved in a mixture of PEG 400 and water. Omeprazole is more rapidly absorbed and to a somewhat greater extent from the buffered solution than from an equivalent dose of enteric-coated granulate used in the clinic. The relative systemic availability of the granulate compared to the solution is about 0.7 (Å Pilbrant, personal communication).

STUDIES IN YOUNG INDIVIDUALS

Balance study

The mean plasma concentration-time curves following the intravenous and oral doses of omeprazole are shown in Fig. 1. Following the oral dose, omeprazole was rapidly absorbed and the maximum concentration was attained within a mean of 13.8 minutes (range 11–25 minutes). The fraction of the oral dose available to the systemic circulation varied from 24.9% to 117.0% (mean 53.6%). The plasma levels of the intravenous dose declined bi-exponentially with time in all eight subjects.

Some pharmacokinetic data derived from the intravenous dose are given in Table I. The mean half-life of the initial phase ($t_{½\alpha}$), representing

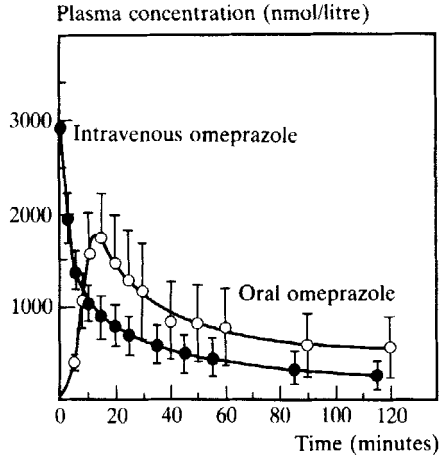

Fig. 1. Mean plasma concentrations of omeprazole in eight young healthy subjects following administration of single doses of 10 mg (28.95 μmol) i.v. and 20 mg (57.90 μmol) p.o. The bars indicate SEM.

Table I. Disposition characteristics of omeprazole in eight young healthy subjects following intravenous administration of 10 mg. The values are means ±SD.

Characteristic	Value
$t_{½\alpha}$	3.0 ± 0.8 minutes
V_c	0.079 ± 0.030 litres/kg
$t_{½\beta}$	0.87 ± 0.74 hours
V_β	0.31 ± 0.09 litres/kg
Total plasma clearance	530 ± 289 ml/minute

distribution of omeprazole to extravascular sites, was 3.0 ± 0.8 minutes, and the volume available for instantaneous distribution (V_C) was 0.079 ± 0.030 litres/kg, that is, comparable with the blood volume. The volume of distribution at apparent distribution equilibrium (V_β) was relatively small. The mean V_β was 0.31 ± 0.09 litres/kg, which would be compatible with localization of a major fraction of the omeprazole dose in the extracellular water, and restriction of about 25% of the total body content of omeprazole to the blood.

The mean half-life of the terminal phase of the plasma concentration-time curve ($t_{½\beta}$) was 52.2 ± 44.4 minutes and the mean total plasma clearance was 530 ± 289 ml/minute. When it is considered that in man the mean ratio between the concentration of omeprazole in whole blood and plasma is about 0.58, the mean total body clearance of omeprazole is about 900 ml/minute, which places the drug among the high clearance compounds.

Insignificant amounts of unchanged radiolabelled drug were excreted via the kidneys and in the stools, but a mean of about 80% of the intravenous and oral doses was excreted as metabolites via the kidneys over a 4-day period (Fig. 2). During the same period of time, faecal excretion accounted for approximately 20% of the doses given. Renal excretion of metabolites appears initially to be very rapid, as about 60% of the radioactive dose is recovered in the urine in the first 6–8 hours after administration.

The metabolic pattern of ^{14}C-labelled omeprazole in pooled urine from five healthy subjects determined by high pressure liquid chromatography (HPLC) is shown in Fig. 3. The existence

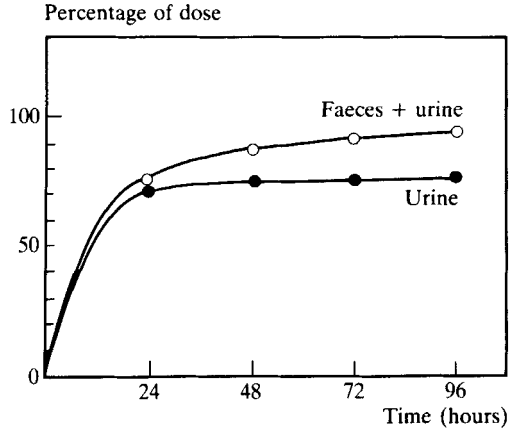

Fig. 2. Recovery of radioactivity in faeces and urine following oral administration of ^{14}C-omeprazole, 20 mg.

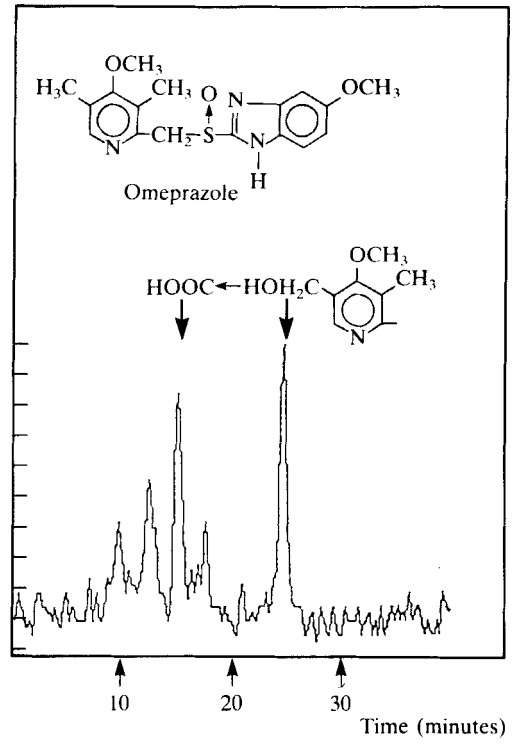

Fig. 3. Metabolic pattern of ^{14}C-labelled omeprazole in pooled urine from five healthy subjects derived by gradient elution reversed phase HPLC.

of at least six different metabolites is indicated, of which the two most abundant ones have been identified as hydroxy-omeprazole and its corresponding carboxylic acid. Hydroxy-omeprazole has also been identified in the plasma, together with omeprazole oxidized or reduced at the sulphur atom – the so-called omeprazole sulphone and omeprazole sulphide. The latter, however, is found in only very low concentrations in human plasma. None of these metabolites is considered to contribute to the inhibitory effect of omeprazole on the proton pump in the gastric mucosa.

Pharmacokinetics of different intravenous and oral doses

The potential for dose dependency in omeprazole pharmacokinetics has been studied in ten young healthy male subjects after acute administration of two intravenous and three oral doses of different strengths. Mean values of some pharmacokinetic parameters derived from the two intravenous doses (10 and 40 mg) are given in Table II. Increasing the intravenous dose from

Table II. Disposition characteristics of omeprazole calculated from the plasma levels in ten healthy subjects following a single intravenous dose.

Parameter	Dose	
	10 mg	40 mg
$t½_{\alpha}$ (minutes)	5.31 ± 1.74	5.90 ± 1.43
$t½_{\beta}$ (hours)	0.482 ± 0.040	0.593 ± 0.078
V_c (litres/kg)	0.139 ± 0.027	0.147 ± 0.018
V_{β} (litres/kg)	0.340 ± 0.037	0.373 ± 0.051
AUC (μmol×hours/litre)	0.754 ± 0.042	3.18 ± 0.23
Total plasma clearance (ml/minute)	658 ± 37	663 ± 42

10 mg to 40 mg had no significant effect on any of these parameters. The area under the concentration-time curve (AUC) as well as the maximum concentration following oral administration increased non-linearly with the dose administered (Fig. 4). The AUCs of the 10 mg and 40 mg oral doses, when transformed into systemic availability, represent 40% and 58%, respectively. As omeprazole is well tolerated over a wide dose range, the increase in systemic availability that might occur in the normal therapeutic range for oral doses (20–40 mg) would have negligible clinical implications.

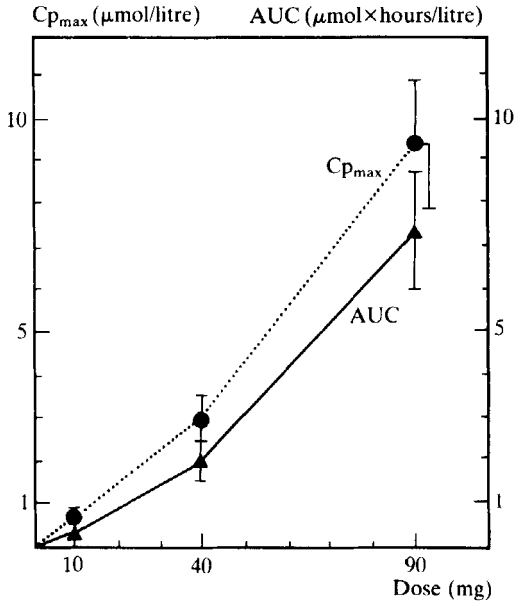

Fig. 4. Relationship between dose, AUC and maximum plasma concentration, Cp_{max}, following administration of three different oral doses of omeprazole. Ten subjects participated and bars indicate SEM.

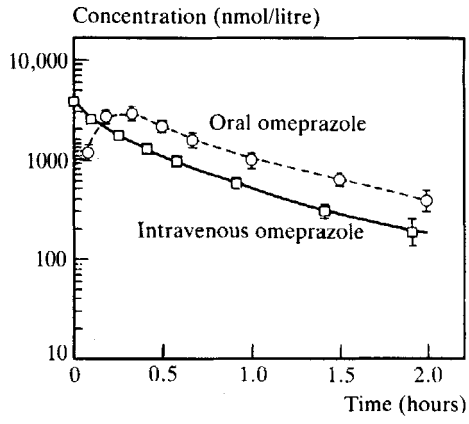

Fig. 5. Mean plasma concentrations of omeprazole following intravenous and oral administration of 20 mg and 40 mg, respectively, to 12 patients with impaired renal function. The bars indicate SEM.

Table III. Disposition characteristics of omeprazole in 12 patients with varying degrees of renal impairment. The data represent mean values ± SD.

Characteristic	Value
$t_{½\alpha}$	7.1 ± 4.1 minutes
Vc	0.173 ± 0.052 litres/kg
$t_{½\beta}$	0.57 ± 0.21 hours
V_β	0.35 ± 0.06 litres/kg
Total plasma clearance	562 ± 218 ml/minute

PHARMACOKINETICS IN PATIENTS WITH IMPAIRED KIDNEY FUNCTION

As omeprazole is eliminated almost entirely by metabolism, impaired renal function would be expected to have negligible effect on the kinetics of omeprazole unless the liver is also affected by the kidney disease. A recently completed study with omeprazole in 12 patients with varying degrees of renal impairment, but with normal liver function data, confirms this hypothesis. The mean plasma concentration–time curves of an acute intravenous and an oral dose of omeprazole, 20 mg and 40 mg respectively, are shown in Fig. 5. The oral dose was rapidly absorbed. The mean time taken to reach maximum concentration was 14.5 ± 6.1 minutes, and the systemic availability reached 68.3 ± 31.6%.

The mean total plasma clearance and V_β were almost identical to those previously obtained in young, healthy individuals (Table III). The mean $t_{½\beta}$ of 0.57 ± 0.21 hours tended to be shorter in these patients than in the subjects with normal renal function (Table I). The longer half-life in the latter group, however, was to a great extent the result of a markedly lower disappearance rate of omeprazole from the plasma in two of the healthy subjects.

As about 80% of an intravenous or oral dose is excreted as metabolites via the kidneys in healthy subjects, impaired renal function was found to have a significant influence on the excretion rate of these metabolites into the urine (Fig. 6).

PHARMACOKINETICS IN HEALTHY ELDERLY SUBJECTS

The effect of age on the absorption and distribution of omeprazole has been studied in a group of eight healthy non-smoking subjects, aged 75–80 years. The doses were 20 mg i.v. and 40 mg p.o.

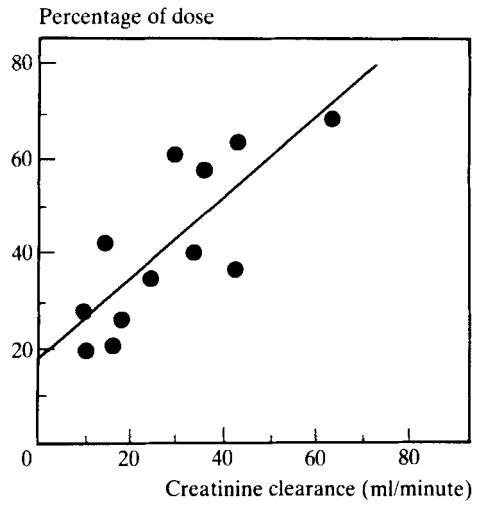

Fig. 6. Accumulated excretion of radioactive metabolites in the urine over a 24-hour period following intravenous administration of ^{14}C-omeprazole to 12 patients with impaired renal function.

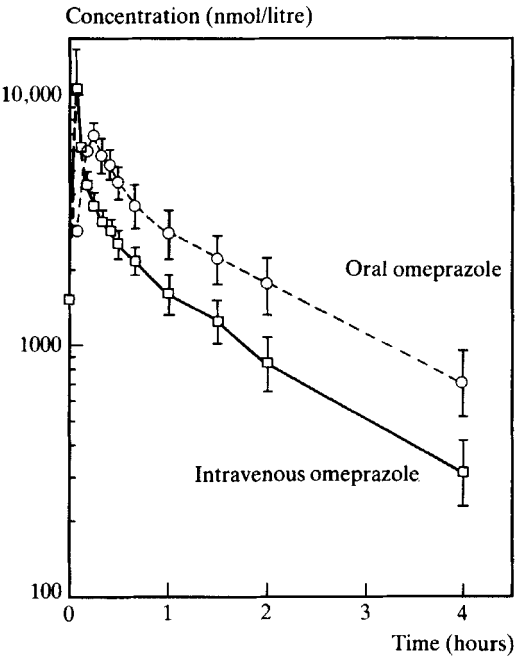

Fig. 7. Mean plasma concentrations of omeprazole in eight healthy elderly subjects following intravenous and oral administration of 20 mg and 40 mg, respectively. The bars indicate SEM.

The concentration of omeprazole in the plasma was followed for 12 hours, and the mean plasma concentration-time profile during the first 4 hours after the administration is shown in Fig. 7; during this time all the subjects still had measurable concentrations of the drug in their plasma.

Similarly to the young individuals, omeprazole was rapidly absorbed in the elderly, with a t_{max} of 15.4 ± 5.0 minutes. The mean maximum concentration of the oral dose was 7.0 ± 2.2 μmol/litre, and a mean of 81.9 ± 21.3% of this dose reached the general circulation. Among the distribution parameters, V_β was smaller (0.24 ± 0.04 litre/kg) than previously found in young healthy subjects and in patients with renal failure. The mean $t_{½\beta}$ was 1.23 ± 0.62 hour and total plasma clearance was 200 ± 105 ml/minute.

The values of these distribution characteristics suggest that increasing age affects the pharmacokinetics of omeprazole to some extent. Further studies in elderly subjects, however, are desirable both from a pharmacokinetic and from a clinical point of view, in order to verify the results of this study and to elucidate its clinical implications.

OMEPRAZOLE AND DRUG INTERACTIONS

In the last few months, two papers have been published on the potential inhibitory effects of omeprazole on the metabolism of some other drugs. The first study investigated the influence of omeprazole on diazepam pharmacokinetics (7). A 2.5-fold prolongation of the $t_{½\beta}$ of diazepam and a corresponding decrease in total plasma clearance were reported, suggesting that omeprazole inhibits the biotransformation of diazepam to at least the same extent as cimetidine does. Omeprazole and cimetidine have been reported to be equipotent inhibitors on a molar basis of some cytochrome P_{450} mediated metabolic reactions (8). The daily dose of cimetidine is 25–50-fold greater than that of omeprazole, and so the relatively pronounced effect of omeprazole on diazepam elimination was somewhat unexpected.

The clinical implication of this interaction is so far unknown, but might be of minor importance. Recent results with cimetidine and diazepam suggest, for example, that the elevated plasma concentrations of diazepam achieved during concomitant cimetidine treatment do not lead to an increased incidence of side-effects compared to administration of diazepam alone (9).

The inhibition of aminopyrine and antipyrine elimination by concomitant omeprazole therapy appears to be much less pronounced than the effect of diazepam kinetics. Henry *et al.* (10) have reported that a dose of omeprazole, 60 mg/day for 2 weeks, prolonged the aminopyrine half-life by 21% and the half-life of antipyrine by 10%. Furthermore, a relatively weak effect of omeprazole on the distribution of phenytoin has recently been reported (R Gugler, personal communication). These results do not correspond to the idea of omeprazole being a potent inhibitor of metabolic reactions. Perhaps the reactions involved in the demethylation of diazepam are particularly affected by the presence of omeprazole at the metabolic sites.

Further studies focusing on the interference of omeprazole with the pharmacokinetics of diazepam and other drugs have been scheduled in a comprehensive programme, which will be initiated as soon as clinical trials with omeprazole resume.

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