Eur J Clin Pharmacol (1990) 39: 195–197

European Journal of Clinical Pharmacology

Pharmacokinetics of various single intravenous and oral doses of omeprazole

T. Andersson, C. Cederberg, C.-G. Regårdh, and I. Skånberg

Research Laboratories, AB Hässle, Mölndal, Sweden

Received: October 20, 1989/Accepted in revised form: February 7, 1990

Summary. The influence of dose on the kinetics of omeprazole and two of its metabolites, hydroxyomeprazole and the sulphone, has been studied. Ten healthy subjects were given omeprazole 10 and 40 mg iv and 10, 40 and 90 mg orally.

No significant dose-related difference in any parameter calculated from the iv experiments was detected. Following the oral solutions, however, there was a dose-dependent increase in systemic availability, probably due to saturable first-pass elimination. The AUC of the sulphone also seemed to increase non-linearly with increasing dose, and that of the hydroxyomeprazole increased in proportion to dose.

The slight dose-dependency of the bioavailability of the solution is considered to be of no or limited clinical relevance. Furthermore, since omeprazole is given orally as slowly absorbed enteric coated granules in the dose of 20 mg o.d., the potential for dose-dependent kinetics in clinical practice would be much less than in the present study.

Key words: Omeprazole, metabolites, bioavailability, pharmacokinetics, dose-dependent kinetics

Omeprazole effectively suppresses gastric acid secretion by inhibiting the H^+, K^+-ATPase in the parietal cell [1, 2]. The degree of acid suppression is correlated with the area under the plasma concentration-time curve (AUC) of omeprazole [3]. Omeprazole is rapidly and completely metabolised by the liver and the major plasma metabolites are hydroxyomeprazole and the sulphone. Approximately 80% is excreted in the urine, the major urinary metabolites being hydroxyomeprazole and its corresponding carboxylic acid [4]. The remaining dose fraction is recovered in the faeces after being excreted mainly via the bile [5].

The pharmacokinetics of omeprazole in man has previously been reviewed [6, 7]. Some data from the present study were presented in those reviews, but this report provides all the results, including information about the metabolites.

The aim of the study was to investigate the influence of dose on the kinetics of omeprazole and two of its metabolites in plasma.

Subjects and methods

Ten healthy males, aged 19–27 y, weighing 70–86 kg, completed the study, which was approved by the local Ethics Committee, and by the Board of Health and Welfare. Informed consent was obtained from each subject.

The study was open in type. It comprised five experiments (doses 10, 40, 90 mg oral and 10, 40 mg iv) in randomised order, each separated by at least 6 days. Omeprazole was dissolved in a mixture of polyethyleneglycol 400 and diluted with $NaHCO_3$ in water. Sodium bicarbonate was given prior to, together with and after drug administration, in a total amount of 48 mmol.

Each experiment started at about 08.00 h with the subject fasting. Blood samples were collected prior to and at intervals for 8 h after dosing. The samples were collected in heparinised tubes, centrifuged and the plasma stored at −20°C until analysed. The concentrations of omeprazole and its metabolites in plasma were determined by liquid chromatography with UV-detection [8, 9]. Standardised meals were served at 2.5 and 5 h.

The plasma profiles following the iv doses were fitted to a biexponential function using the NONLIN program. The constants associated with the two-compartment model were determined, and various pharmacokinetic parameters, such as AUC, total plasma clearance (CL), volumes of distribution (V_c, V_z), half-life of distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2}$), and systemic availability of each oral doses (f), were calculated according to standard methods.

The statistical significance of the influence of dose on the various pharmacokinetic parameters studied was determined by Student's t-test for paired observations, or by two-way ANOVA followed by Scheffe's contrast U-test. $P < 0.05$ was considered statistically significant.

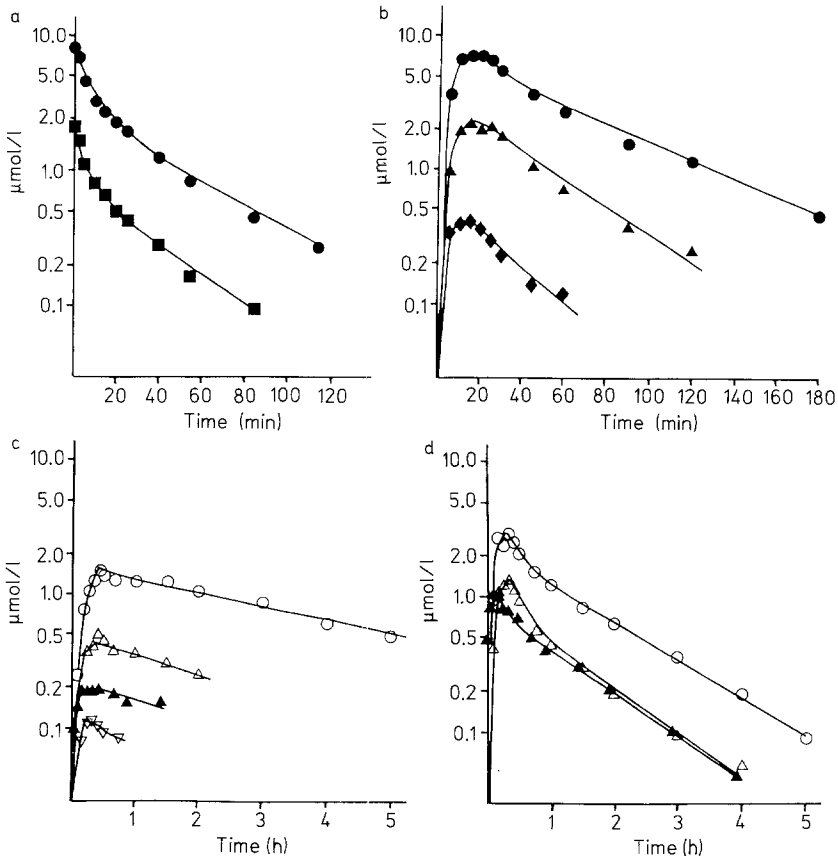

Fig. 1. Mean plasma concentration-time profiles of omeprazole following (a) administration of 10 (-■-) and 40 (-●-) mg i.v., and (b) oral administration of 10 (-◆-), 40 (-▲-) and 90 (-●-) mg ($n = 10$); (c) Mean plasma concentrations of the "sulphone" following omeprazole 40 mg iv (-▲-) and 10 (-▽-), 40 (-△-) and 90 (-○-) mg p.o. ($n = 10$); and (d) "Hydroxyomeprazole" following omeprazole 40 mg iv (-▲-) and 40 (-△-) and 90 (-○-) mg orally ($n = 5$)

Results

Omeprazole

The mean plasma concentrations of omeprazole are shown in Fig. 1, and pharmacokinetic parameters derived from the individual plasma concentrations are presented in Table 1. Omeprazole was rapidly distributed into a relatively small volume for both intravenous doses. The half-life of omeprazole in the terminal phase of the plasma concentration-time curve ($t_{1/2}$) ranged from 0.3 to 1.0 h, with the corresponding volume of distribution ranging from 0.2 to 0.6 $l \cdot kg^{-1}$. The plasma clearance varied two-fold between individuals. There was no influence of dose on any pharmacokinetic parameter studied.

Following *oral* administration, the maximum plasma concentration (C_{max}) was attained within 0.5 h. The values of C_{max} and AUC increased nonlinearly with increasing oral dose, and bioavailability increased from 40 to 58% as the dose rose from 10 to 40 mg ($P < 0.05$). f for the 90 mg dose was not calculated due to lack of an iv reference value. The mean elimination half-life from plasma was longer for the 90 mg dose than for the two lower doses.

Omeprazole sulphone

Its plasma concentrations following the 10 mg iv dose were close to the minimum determinable concentration (≤ 50 nmol $\cdot l^{-1}$). C_{max} was reached on average within 0.5 h (Fig. 1 c; Table 2). The mean $t_{1/2}$ varied between 1.3 and 2.2 h and was longest for the 90 mg oral dose. The mean AUC for the intravenous 40 mg dose was about 40% lower than that for the corresponding oral dose. The mean AUCs of the oral doses increased non-linearly with increasing dose.

Hydroxyomeprazole

The plasma concentrations of hydroxyomeprazole in 5 subjects following iv administration of 40 mg and oral administration of 40 and 90 mg omeprazole are shown in Fig. 1 d. The mean C_{max} of hydroxyomeprazole increased linearly (Table 2) with the oral dose. The mean $t_{1/2}$ was 1 h and was independent of dose. The mean AUC of hydroxyomeprazole was approximately the same following the 40 mg iv and oral doses, and it increased in proportion to the oral dose.

Discussion

Intravenous administration resulted in rapid initial distribution into a central compartment with a mean volume of about 10 l, followed by a distribution into an apparent volume approximating the volume of the extracellular water. Omeprazole was rapidly eliminated. Plasma clearance varied only twofold in the present study, while the corresponding intersubject variability was 14-fold in a previous study [10]. There was no slow metaboliser of omeprazole here, although there were two in the previous study.

Omeprazole was rapidly absorbed following all oral doses and its bioavailability was increased after higher

Table 1. Pharmacokinetics of omeprazole calculated from the plasma levels following single iv doses of 10 and 40 mg and single oral doses of 10, 40 and 90 mg ($n = 10$)

Parameter	10 mg			40 mg			90 mg		
	mean	SD	range	mean	SD	range	mean	SD	range
iv $t_{1/2\alpha}$ (min)	5.3	5.5	1.3–18	5.9	4.5	1.6–16			
$t_{1/2}$ (h)	0.48	0.13	0.28–0.79	0.59	0.25	0.32–1.0			
V_c (l/kg)	0.14	0.09	0.02–0.28	0.15	0.06	0.07–0.23			
V_z (l/kg)	0.34	0.12	0.21–0.54	0.37	0.16	0.21–0.62			
AUC (μmol × h/l)	0.75	0.13	0.58–0.96	3.18	0.73	2.27–4.82			
CL (ml/min)	658	117	503–835	633	133	400–850			
po t_{max} (h)	0.21	0.06	0.17–0.33	0.28	0.09	0.17–0.42	0.32	0.18	0.17–0.75
C_{max} (μmol/l)	0.55	0.37	0.14–1.24	3.0	1.61	1.4–6.4	9.4	4.9	3.6–17
$t_{1/2}$ (h)	0.40[a]	0.16	0.20–0.63	0.49	0.16	0.28–0.70	0.75	0.35	0.45–1.6
AUC (μmol × h/l)	0.31[a]	0.20	0.13–0.69	2.0	1.33	0.70–5.0	7.4	4.5	3.1–16
f	0.40[a]	0.23	0.15–0.73	0.58	0.25	0.29–1.05			

[a] $n = 9$

Table 2. Pharmacokinetic parameters of (S) omeprazole-sulphone ($n = 10$) and (H) hydroxyomeprazole ($n = 5$) calculated from the plasma levels following single iv and oral doses of omeprazole

Parameter	40 mg-iv		10 mg-oral		40 mg-oral		90 mg-oral	
	mean	SD	mean	SD	mean	SD	mean	SD
S t_{max} (h)	0.47	0.24	0.38	0.16	0.40	0.09	0.58	0.38
C_{max} (μmol/l)	0.232	0.108	0.122	0.060	0.531	0.179	1.797	1.06
$t_{1/2}$ (h)	1.85	0.74	1.84	0.76	1.33	0.72	2.21	1.11
AUC (μmol × h/l)	0.744	0.740	0.248	0.093	1.195	1.132	6.602	6.03
H t_{max} (h)	0.17	0.047			0.32	0.038	0.25	0.103
C_{max} (μmol/l)	1.234	0.156			1.396	0.433	3.130	0.361
$t_{1/2}$ (h)	0.91	0.080			0.99	0.078	1.03	0.192
AUC (μmol × h/l)	1.239	0.182			1.406	0.266	3.111	1.815

doses, probably as a result of saturable first-pass elimination. However, linearity was obtained when omeprazole was administered as enteric coated granules in the dose range 10 to 40 mg (Andersson, unpublished data), which can be explained by differences between the absorption rates of the diverse formulations.

From the present study it was concluded that the kinetics following iv administration was linear in the dose-range 10–40 mg, but that the bioavailability increased with increasing oral dose. The two metabolites studied exhibited different kinetics; hydroxyomeprazole showed linear kinetics as regards AUC and the oral dose of omeprazole, while the omeprazole sulphone exhibited non-linearity, like the parent drug.

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T. Andersson
Gastrointestinal Research
Clinical Pharmacology and Medicine
AB Hässle
S-43183 Mölndal
Sweden