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Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects

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1 Ten healthy subjects were given 20 mg omeprazole EC (enteric coated) granules once daily for 8 days. An i.v. tracer dose of [^{14}C]-omeprazole was given simultaneously with the first and last oral doses and blood sampling was performed thereafter. In order to study the extent of absorption at minimal acid exposure, a single dose of 20 mg omeprazole was also given as a buffered solution, before and after the treatment with EC granules.
2 Kinetic parameters of omeprazole after the i.v. tracer dose were unchanged on repeated dosing while AUC increased by approximately 40% for the solution and 60% for the EC granules.
3 The increased AUC is caused by an increased systemic availability, which may be explained by a decreased first-pass elimination during repeated treatment and/or by a reduced degradation of omeprazole in the stomach secondary to the profound decrease in intragastric acidity caused by the drug.
4 The implication of these findings is that the antisecretory effect of therapeutic doses of omeprazole must be studied during repeated administration and not judged from studies using single doses only.

Keywords omeprazole substituted benzimidazole proton pump inhibitor bioavailability kinetics repeated dosing

Introduction

Omeprazole, a substituted benzimidazole, has been shown to suppress gastric acid secretion by inhibiting the H^+,K^+-ATPase in the parietal cell (Fellenius *et al.*, 1981; Wallmark *et al.*, 1985). The degree of suppression of gastric acid secretion is correlated with the area under the plasma omeprazole concentration-time curve (AUC), but is not related directly to the time course of plasma drug concentration (Lind *et al.*, 1983). The antisecretory effect is dose-dependent and long-lasting. Despite the fact that omeprazole is eliminated rapidly from plasma (half-life is usually less than 1 h) it is still effective 24 to 72 h after a single dose (Lind *et al.*, 1983). The effective control of acid secretion by omeprazole results in a rapid healing of peptic ulcers and erosive reflux oesophagitis. In this respect, omeprazole is more effective than H_2-receptor antagonists (Bardhan *et al.*, 1986; Hetzel *et al.*, 1988; Klinkenberg-Knol *et al.*, 1987; Walan *et al.*, 1989).

The drug is degraded in acidic media. Therefore, an acid resistant formulation consisting of enteric-coated (EC) granules of omeprazole has been developed for oral use. Repeated once-daily administration of these granules for 5

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days resulted in an increased AUC-value following a 40 mg dose (Prichard *et al.*, 1985). The reasons for the increase in AUC during repeated dosing were not explored by Prichard *et al.* (1985) but several possibilities arise, for instance, increased stability of the formulation due to the increase in pH of the gastric juice produced by repeated dosing and decreased first-pass elimination and/or systemic clearance during repeated administration.

This study was performed to explore the potential mechanisms for the increased AUC observed after repeated administration of omeprazole as EC granules.

Methods

Ten healthy (based on physical examination, ECG and a laboratory screen) males aged 24–34 years and weighing 68–85 kg completed the study. The study was conducted in accordance with the 'Declaration of Helsinki' and was approved by the Ethics and Isotope Committees of the Medical Faculty of the University of Göteborg and by the Swedish National Board of Health and Welfare. Written consent was obtained from each subject prior to participation in the study.

The study was performed as an open study and each subject participated in one study period, consisting of four separate experiments, extended over at least 17 days. A single dose of 20 mg omeprazole as a buffered solution was given at least 7 days before and 1 day after 8 days' treatment with 20 mg omeprazole as EC granules once daily. An i.v. tracer dose of [^{14}C]-omeprazole was given together with the first and last dose of the EC granules.

To prepare the i.v. tracer dose [^{14}C]-labelled omeprazole (20 μCi; 0.12 mg omeprazole) was dissolved in a mixture of polyethylene glycol (PEG) 400 and sterile $NaHCO_3$ to a final volume of 10 ml. The infusion rate was 2 ml min^{-1}. To prepare the buffered solution 20 mg of omeprazole was dissolved in 20 g PEG 400 and diluted prior to use with 50 ml of a $NaHCO_3$ solution (8 mmol 50 ml^{-1}). In order to protect the drug from gastric acid exposure the buffered solution was given together with 48 mmol (300 ml) $NaHCO_3$. The solid dose of 20 mg omeprazole was given as EC granules in a hard gelatin capsule. The capsule was swallowed with ~250 ml of water daily before breakfast for 8 days.

Each experiment started at about 08.00 h with the subjects having abstained from all food and liquids from 22.00 h the previous day. Blood samples (5 ml) for assay of omeprazole were collected from an antecubital vein by an indwelling catheter prior to and 5, 10, 15, 20, 25, 30, 45 min and 1, 1.5, 2, 3, 4, 5 and 6 h after the two administrations of the oral solution. In the two experiments with EC granules given in combination with the i.v. tracer dose blood samples were taken prior to and 5, 7, 10, 15, 20, 25, 30, 45 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h after dosing. The blood samples were collected in heparinised tubes, kept at room temperature for at least 5 min and then centrifuged for 10 min. The plasma was transferred to plastic tubes and stored at −20° C until analysis. Standard meals were served 2.5 and 6 h after the oral solutions and 2.5, 6 and 10 h after the combined oral and i.v. doses.

Alcohol and all medication, including 'over the counter drugs', were not allowed for 2 days prior to the first experiment and for 2 days prior to the second experiment and throughout the study. The routine laboratory screen was repeated after the last experiment.

The concentrations of [^{14}C]-omeprazole and unlabelled omeprazole in plasma were measured by reversed-phase liquid chromatography followed by liquid scintillation counting and u.v.-detection, respectively. The liquid chromatographic system consisted of an LC-pump (Beckman 110A), an autosampler with a 150-μl loop (Waters WISP 710B), a stainless steel column (150 × 4.6 mm) packed with Polygosil C18, 5 μm, a precolumn (30 × 4.6 mm) containing Brownlee RP18, 5 μm, and an LC-detector (LDC Spectromonitor III) operated at 302 nm. The aqueous mobile phase contained 33% (v/v) acetonitrile and 7% (v/v) phosphate buffer (pH 8.0, I = 0.5). The flow-rate was 1.0 ml min^{-1}. The liquid scintillation counting was performed in a Beckman LS 3800 spectrometer. The following procedure was used: To 1.00 ml of plasma were added 100 μl of phosphate buffer (pH 7.0, I = 1.0) and 100 μl of the internal standard (an omeprazole analogue). Omeprazole was extracted into 5.00 ml of dichloromethane. 4 ml of the extract was transferred to a conical tube and evaporated to dryness. The residue was dissolved in 500 μl of a mixture of acetonitrile and phosphate buffer (pH 7.5, I = 0.05), 20:80 (v/v). 150 μl was injected onto the chromatographic column. The fraction corresponding to the u.v. peak of unlabelled omeprazole was collected in scintillation vials, 10 ml Insta-Gel was added and the radioactivity was measured by liquid scintillation counting. Correction for quenching was made by external standardization. The limit of determination was 2 nmol l^{-1} of plasma (0.6 ng ml^{-1}) for [^{14}C]-omeprazole, cor-

responding to a d min^{-1} value twice that of the blank. Unlabelled omeprazole was measured from the u.v.-trace. The relative standard deviation was 1.9 and 2.6% at 1700 and 170 nmol l^{-1}, respectively, and the limit of determination (rel. s.d. < 10–15%) was 50 nmol l^{-1} (15 ng ml^{-1}; Lagerström & Persson, 1984).

The elimination half-lives ($t_{½}$) of omeprazole following administration of the i.v. tracer dose and buffered solution of the drug were calculated by linear regression of the terminal portion of individual log plasma drug concentration-time curves. The area under the plasma drug concentration-time curve (AUC) was measured by the linear trapezoidal rule and, in the case of the tracer dose and buffered solution, extrapolated to infinity using the last measurable plasma drug concentration and the disposition rate constant of the terminal phase.

The values of the last measurable plasma drug concentrations and $t_{½}$ indicated that omeprazole would have been undetectable at 24 h after dose. Hence the plasma clearance (CL) was calculated from dose (i.v.)/AUC (i.v.).

The bioavailability (F) of omeprazole following oral administration was calculated from:

$$F = \frac{AUC_{oral}}{AUC_{i.v}} \times \frac{dose_{i.v.}}{dose_{oral}}$$

For the buffered solution, F before treatment was calculated using the AUC values of the i.v. tracer dose from the first day of treatment and F after treatment by using the AUC values of the i.v. tracer dose from the last day of treatment.

The AUC, F and $t_{½}$ values were log-normally distributed and 95% confidence intervals for the expected values of the logarithms were calculated, which then were transformed to 95% confidence intervals in the original scale. This gave a consistent estimate of both the median and the geometric mean in the hypothetical parent population of subjects. The CL values, however, were considered to be normally distributed and arithmetic means with 95% confidence intervals were calculated. The changes in the pharmacokinetic parameters before and after 8 days' treatment with omeprazole were expressed by confidence intervals for the mean ratios—calculated as either geometric or arithmetic mean—and statistical significance (P < 0.05) was reached when this confidence interval did not include 1.00.

Results

No adverse events were observed by the nursing/medical staff or reported by the subjects during the experiments. All 10 subjects completed the study according to the protocol.

I.v. tracer dose

The median plasma concentration-time profiles of omeprazole following the i.v. tracer dose on the two dosing occasions together with the profiles for subjects with the highest and lowest AUC values are shown in Figure 1. Individual pharmacokinetic parameters are given in Table 1.

The values of AUC, $t_{½}$ and CL following the two administrations of the i.v. omeprazole tracer dose showed a five- to six-fold variation between subjects. However, there were no significant changes in AUC, $t_{½}$ or CL between day 1 and day 8. The mean values of $t_{½}$ and CL were

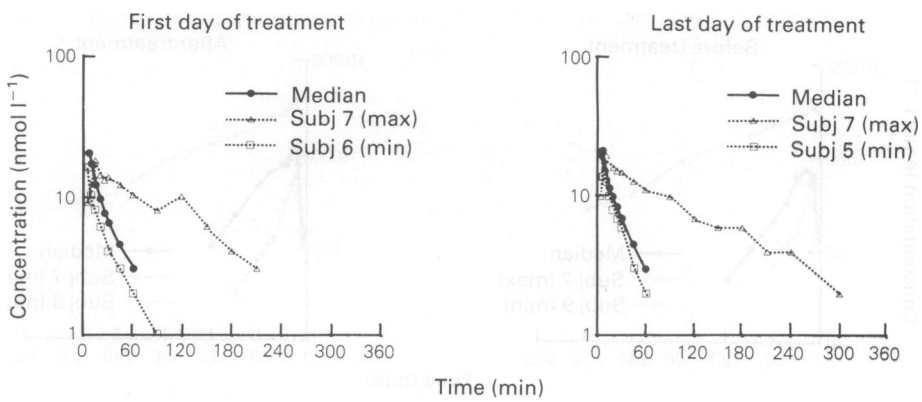

Figure 1 Median plasma concentration-time profiles of omeprazole after administration of an i.v. tracer dose on the first and last day of 8 days' oral treatment with omeprazole as EC granules, 20 mg, in 10 healthy subjects. The extreme profiles observed in individual subjects are also displayed.

0.5 h and 0.5 l min^{-1}, respectively, on both occasions.

Oral administration—buffered solution

The median plasma concentration-time profiles of omeprazole following administration of the buffered solution together with the profiles for subjects with the highest and lowest AUC values are shown in Figure 2. Individual pharmacokinetic parameters are given in Table 2.

The AUC values showed a large variation between subjects, whereas the $t_{½}$ values varied much less. The AUC value was significantly higher when the buffered solution was given after 8 days' treatment with EC granules compared with before treatment, the mean ratio being 1.39. The $t_{½}$ was not significantly changed. The *F* value was increased, although not significantly, from an average of 0.40 before to 0.52 after treatment, the mean ratio being 1.29.

Oral administration—EC granules

The median plasma concentration-time profiles of omeprazole following administration of the EC granules together with the profiles for subjects with the highest and lowest AUC values are

Table 1 Individual values of the area under the plasma concentration-time curve (AUC), elimination half-life ($t_{½}$) and clearance (CL) of omeprazole after an i.v. tracer dose administered on the first and last day of 8 days' treatment with oral omeprazole as EC granules, 20 mg, in 10 healthy subjects

	AUC (nmol l^{-1} h)		$t_{½}$ *(h)*			*CL (ml min^{-1})*		
Subject	*First day (B)*	*Last day (A)*	*First day (B)*	*Last day (A)*		*First day (B)*	*Last day (A)*	*CL A/B*
1	15.57	18.23	0.47	0.84		360	308	0.86
2	11.03	9.38	0.51	0.37		508	598	1.18
3	9.19	9.55	0.43	0.34		610	587	0.96
4	15.96	23.13	0.56	0.64		351	242	0.69
5	7.40	7.39	0.34	0.32		757	758	1.00
6	7.08	11.18	0.44	0.68		792	475	0.60
7	37.81	42.66	1.53	1.67		148	131	0.89
8	13.64	12.18	0.52	0.45		411	460	1.12
9	7.31	8.45	0.47	0.38		767	664	0.87
10	9.49	8.52	0.32	0.32		591	658	1.11
Geometric mean	11.68	12.86	0.50	0.52	Arithmetic mean	529	488	0.93
95% confidence interval	8.11–16.82	8.65–19.10	0.37–0.68	0.35–0.76	95% confidence interval	377–682	342–634	0.79–1.06
Range	7.08–37.81	7.35–42.66	0.32–1.53	0.32–1.67	Range	148–792	131–758	0.60–1.18
Geometric mean A/B	1.10		1.03					
95% confidence interval	0.94–1.29		0.83–1.26					

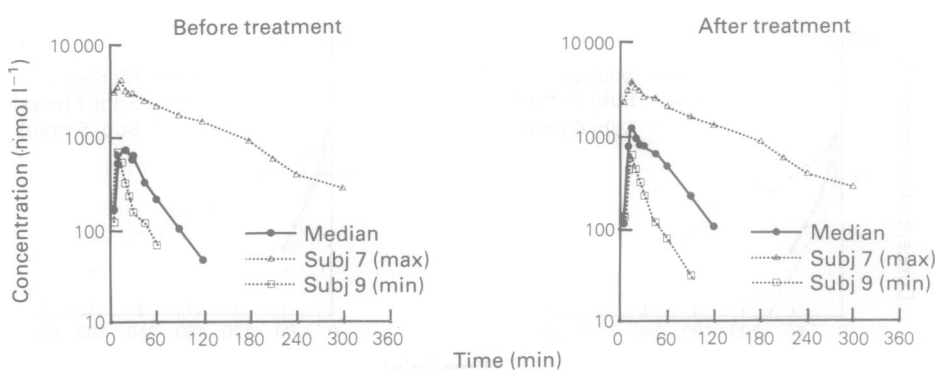

Figure 2 Median plasma concentration-time profiles after oral administration of 20 mg omeprazole as a buffered solution 1 week before and 1 day after 8 days' oral treatment with omeprazole as EC granules, 20 mg (n = 10). The extreme profiles observed in individual subjects are also displayed.

Table 2 Individual values of the area under the plasma omeprazole concentration-time curve (AUC), elimination half-life ($t_{½}$) and bioavailability (F) after administration of an oral solution of 20 mg omeprazole, administered 1 week before and again 1 day after 8 days' treatment with oral omeprazole as EC granules, 20 mg, in 10 healthy subjects

	AUC (nmol l^{-1} h)		$t_{½}$ *(h)*		F	
Subject	*Before treatment (B)*	*After treatment (A)*	*Before treatment (B)*	*After treatment (A)*	*Before treatment (B)*	*After treatment (A)*
1	1307	2598	0.55	0.83	0.49	0.82
2	429	928	0.34	0.47	0.21	0.54
3	800	1130	0.54	0.45	0.48	0.65
4	2928	2994	0.76	1.00	1.07	0.76
5	460	615	0.50	0.37	0.35	0.46
6	415	510	0.41	0.41	0.32	0.25
7	8275	7760	1.68	1.77	1.21	0.99
8	600	773	0.45	0.50	0.25	0.36
9	269	287	0.41	0.39	0.19	0.19
10	557	1177	0.50	0.48	0.31	0.78
Geometric mean	845	1179	0.55	0.58	0.40	0.52
95% confidence interval	399–1790	590–2357	0.40–0.76	0.40–0.84	0.25–0.63	0.35–0.76
Range	269–8275	287–7760	0.34–1.68	0.37–1.77	0.19–1.21	0.19–0.99
Geometric mean A/B:	1.39			1.06	1.29	
95% confidence interval	1.12–1.73			0.90–1.25	0.93–1.79	

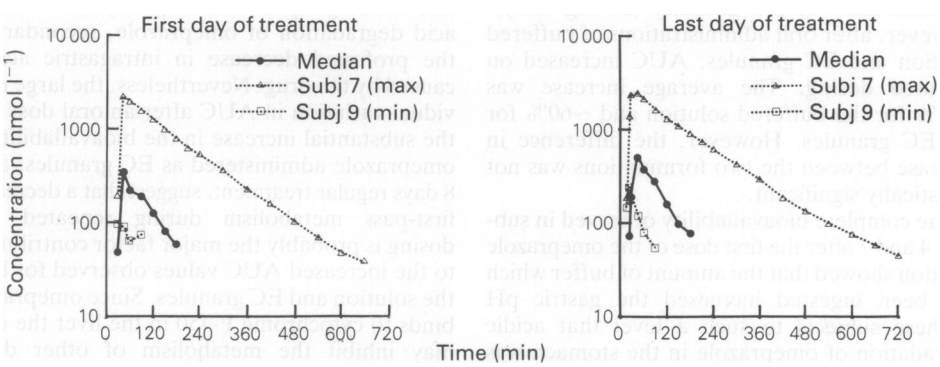

Figure 3 Median plasma concentration-time profiles measured on the first and last days of 8 days' oral treatment with 20 mg omeprazole as EC granules (n = 10). The extreme profiles observed in individual subjects are also displayed.

shown in Figure 3. The individual availability data are given in Table 3.

As after administration of the buffered solution, AUC values following administration of EC granules showed a large inter-individual variation. The AUC increased significantly from the first to the last day of 8 days' treatment with EC granules, with a mean ratio of 1.61. The F value also increased significantly from an average of 0.25 on the first to 0.36 on the last day of treatment, with a mean ratio of 1.45.

Discussion

The results from the i.v. tracer dose experiments indicated that the systemic elimination of an i.v. dose of omeprazole is unaltered by repeated

Table 3 Individual values of the area under the plasma omeprazole concentration-time curve (AUC) and bioavailability of omeprazole measured on the first and last day of 8 days' treatment with oral omeprazole as EC granules, 20 mg, in 10 healthy subjects

	AUC (nmol l^{-1} h)		F	
Subject	*First day (B)*	*Last day (A)*	*First day (B)*	*Last day (A)*
1	1040	1783	0.40	0.59
2	872	691	0.47	0.44
3	326	794	0.21	0.50
4	1206	2272	0.45	0.59
5	210	300	0.17	0.24
6	234	330	0.20	0.17
7	5326	6559	0.85	0.92
8	334	533	0.15	0.26
9	81	145	0.07	0.10
10	270	702	0.17	0.49
Geometric mean	482	775	0.25	0.36
95% confidence interval	207–1122	351–1711	0.15–0.42	0.22–0.58
Range	81–5326	145–6559	0.07–0.85	0.10–0.92
Geometric mean A/B	1.61		1.45	
95% confidence interval	1.26–2.05		1.10–1.90	

administration of EC granules (20 mg daily). However, after oral administrations of buffered solution and EC granules, AUC increased on repeated dosing. The average increase was ~40% for the buffered solution and ~60% for the EC granules. However, the difference in increase between the two formulations was not statistically significant.

The complete bioavailability observed in subjects 4 and 7 after the first dose of the omeprazole solution showed that the amount of buffer which had been ingested increased the gastric pH in these subjects to such a level that acidic degradation of omeprazole in the stomach was avoided. However, in subject 2 a doubling in AUC value was observed for the solution with a somewhat lower AUC value for the EC granules together with an almost unchanged CL of the i.v. dose following repeated dosing, which indicated that the buffering capacity after the first dose of the solution was not sufficient in this subject. Thus, the results from this study show that the buffering capacity of the solution was insufficient to prevent acidic degradation of omeprazole in some subjects at single dose administrations. Consequently, one explanation for the increased AUC values observed for the omeprazole solution during repeated dosing may be decreased acid degradation of omeprazole, secondary to the profound decrease in intragastric acidity caused by the drug. Nevertheless, the large individual variation in AUC after an oral dose and the substantial increase in the bioavailability of omeprazole administered as EC granules, after 8 days regular treatment, suggest that a decreased first-pass metabolism during repeated oral dosing is probably the major factor contributing to the increased AUC values observed for both the solution and EC granules. Since omeprazole binds to cytochrome P-450 in the liver the drug may inhibit the metabolism of other drugs metabolised by this system (Gugler & Jensen, 1985). Thus, a decreased first-pass metabolism during repeated omeprazole dosing might be explained by omeprazole acting as an inhibitor of its own metabolism. Against this, however, it should be noted that no omeprazole was detectable in plasma at the time of ingestion of the last dose. However, inhibition of the first-pass metabolism of omeprazole on repeated dosing might be mediated by the sulphone metabolite rather than the parent drug. The sulphone product is eliminated more slowly from plasma than omeprazole itself and has been also shown to

inhibit the cytochrome P-450 system *in vitro* (Gugler & Jensen, 1985). Low concentrations of this metabolite have been detected in plasma 24 h after dosing (unpublished data).

In conclusion, we have found that the kinetics of omeprazole when given as an i.v. tracer dose were unchanged after repeated oral dosing with EC granules 20 mg daily, while AUC increased by approximately 40% for the solution and 60% for the EC granules. The increased oral AUC may be explained by a decreased first-pass elimination and/or a decreased degradation of omeprazole in the stomach. The implication of these findings is that the antisecretory effect of therapeutic doses of omeprazole must be studied during repeated administration and not judged from studies using single doses only.

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