Influence of acid secretory status on absorption of omeprazole from enteric coated granules

TOMMY ANDERSSON, ROBERT BERGSTRAND & CHRISTER CEDERBERG
Research Laboratories, AB Hässle, Mölndal, Sweden

- 1 In order to study the absorption of omeprazole under normal acidic conditions in the stomach as well as when the granules are exposed to minimal gastric acid, eight healthy males were given 20 mg omeprazole as enteric coated (EC) granules either alone or 2 h after a ranitidine dose of 300 mg, respectively.
- 2 Blood samples were collected at intervals for 12 h following both omeprazole administrations. The pH was recorded during the first 4 h in half the subjects in each experiment to document the difference in pH during the absorption phase of omeprazole.
- 3 The area under the plasma concentration-time curve, AUC, of omeprazole was virtually the same irrespective of whether or not the granules were exposed to gastric acid. However, the maximum plasma concentration ($C_{\max}$) was higher and the time to reach $C_{\max}$ was shorter when omeprazole was administered after a ranitidine dose.
- 4 It is concluded that gastric acidity has negligible influence on the AUC of omeprazole, which is directly correlated to the antisecretory effect, when administered as EC granules.

Keywords omeprazole substituted benzimidazole acid influence
absorption EC granules

Introduction

Omeprazole, a substituted benzimidazole, has been shown effectively 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 to the area under the plasma concentration-time curve (AUC) of omeprazole and is not directly related to plasma concentration of the drug at any given time (Lind *et al.*, 1983). Despite the fact that omeprazole is rapidly eliminated from plasma with a half-life usually less than 1 h, some effect is still present 24 to 72 h after dose (Lind *et al.*, 1983). The long-lasting binding of the active form of omeprazole to the H^+,K^+ -ATPase in the parietal cells accounts for the lack of correlation between plasma concentration and degree of acid inhibition (Wallmark *et al.*, 1984). The effective control of acid secretion by omeprazole results in a rapid healing of peptic ulcers and erosive reflux oesophagitis and 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).

Omeprazole is acid labile and consequently acid resistant enteric coated (EC) granules, dispensed in

hard gelatin capsules, have been developed to minimise acid degradation in the stomach. Previous studies with repeated once daily oral administration of omeprazole as EC granules in different doses have shown that the AUC increases during the first 4 days of treatment with no further rise thereafter during continued treatment (Andersson *et al.*, 1990; Müller *et al.*, 1983; Prichard *et al.*, 1985). The increase in AUC has also been shown to be dose-dependent between 10 and 40 mg with a more pronounced increase with higher doses (Andersson *et al.*, 1989). Proposed explanations for the higher AUC values obtained during repeated dosing are a decreased hepatic metabolism, primarily first-pass, and/or increased absorption due to an increased stability of the granules as a result of the decreased intragastric acidity during omeprazole treatment. Thus, we were not 100% confident that the enteric coating protected all of the omeprazole dose on the first day of administration. This study was performed to investigate whether a decrease in gastric acidity would lead to higher AUC of orally administered omeprazole, which in turn could answer the question if decreased acidity during repeated dosing could be an explanation of the increased AUCs pre-

viously reported. Reduction of the gastric acid secretion was obtained by pretreatment with ranitidine 300 mg on the preceding evening and again 2 h prior to the omeprazole dose.

Methods

Eight healthy males of median age 28 years (range: 24–48) and median weight 81 kg (range: 70–86) completed the study which was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical Faculty of the University of Göteborg and by the Swedish National Board of Health and Welfare. Written informed consent was obtained from each subject prior to participation.

This study was conducted as a randomised cross-over trial with two experiments separated by at least 1 week's washout. In each experiment omeprazole was administered either alone or 2 h after a ranitidine dose and followed by blood sampling.

Omeprazole 20 mg was given as EC granules dispersed in a hard gelatin capsule. The capsule was swallowed with ~250 ml of water. Ranitidine 2×150 mg (Zantac® tablets) was given in the appropriate experiment at bedtime on the evening before the investigation and a further 2×150 mg were given in the morning 2 h before the omeprazole dose.

Each experiment started at about 08.00 h with the subjects having abstained from all food and liquids since 22.00 h the previous day. Blood samples (5 ml) for assay of omeprazole were collected from an antecubital vein via an indwelling cannula prior to and every 0.5 h for 4 h then every hour for 12 h after omeprazole administration. 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. In subjects 5 to 8 inclusive the pH in the stomach was recorded via an antimony electrode (Synectics®) during the first 4 h after omeprazole dosing in both experiments. Standardised meals were served 2.5, 6 and 10 h after the omeprazole administration. Alcohol and all medication, including 'over the counter' drugs, were not allowed for 2 days prior to each experiment.

The concentrations of omeprazole in plasma were determined at the Department of Bioanalytical Chemistry, AB Hässle, by liquid chromatography and u.v.-detection (Lagerström & Persson, 1984).

The area under the plasma omeprazole concentration-time curve (AUC) was calculated using the linear trapezoidal rule and extrapolated to infinity by adding the residual area obtained by dividing the last measured plasma concentration with the rate constant determined from the terminal slope of the log plasma concentration-time curve ($0.693/t_{1/2}$). Plasma elimination half-life ($t_{1/2}$) was calculated from the regression line of the terminal log plasma concentrations vs time. The maximum plasma concentration ($C_{\max}$) and the time to reach $C_{\max}$ ($t_{\max}$) were recorded. Mean values with 95% confidence intervals are presented for the different pharmacokinetic parameters. Differences in kinetic parameters between the experiments with and without ranitidine are expressed as means with 95% confidence intervals. A

difference is regarded as statistically significant ($P < 0.05$) when the confidence interval does not span 0.00.

Results

Median pH values, with ranges, during the first 4 h of the two experiments are shown in Figure 1. The median pH in the stomach was between 6 and 8 during the first hours of the ranitidine experiment while it was as low as 1–2 when omeprazole was given alone.

The mean plasma concentration-time profiles of omeprazole following administration of the EC granules in the two different experiments are shown in Figure 2,

Figure 1 Median pH values, with ranges, during the 4 h following omeprazole administration in the two experiments ($n = 4$). (○ omeprazole, range; ● omeprazole + ranitidine, ---- range).

Figure 2 Mean ($\pm$ s.e. mean) plasma concentration-time profiles of omeprazole following administration of 20 mg as EC granules alone (—○—) or after ranitidine 300 mg (—●—) in eight healthy subjects.

Table 1 Maximum plasma concentration ($C_{\max}$), time to reach $C_{\max}$ ($t_{\max}$), area under the plasma concentration-time curve (AUC), and elimination half-life ($t_{1/2}$) following single dose administration of 20 mg omeprazole as EC granules either alone or after ranitidine 300 mg, in eight healthy subjects

	$C_{\max}$ ($\mu\text{mol l}^{-1}$)		$t_{\max}$ (h)		AUC ($\mu\text{mol l}^{-1} \text{ h}$)		$t_{1/2}$ (h)	
	Omeprazole (B) + omeprazole (A)	Ranitidine + omeprazole (A)	Omeprazole (B) + omeprazole (A)	Ranitidine + omeprazole (A)	Omeprazole (B) + omeprazole (A)	Ranitidine + omeprazole (A)	Omeprazole (B) + omeprazole (A)	Ranitidine + omeprazole (A)
Mean	0.31	0.48	1.6	0.7	0.54	0.65	0.58	0.59
95% confidence interval	0.20, 0.42	0.37, 0.60	1.1, 2.2	0.5, 0.9	0.34, 0.74	0.45, 0.85	0.51, 0.65	0.54, 0.65
Mean A-B	0.17		-0.9		0.11			0.01
95% confidence interval	0.09, 0.24		-1.4, -0.5		-0.01, 0.24		-0.03, 0.06	
P value	0.001		0.002		0.08		0.48	

and mean pharmacokinetic parameters are presented in Table 1. The maximum plasma concentrations of omeprazole were higher and were reached earlier when the omeprazole dose was given after ranitidine. However, the AUC values were virtually the same, being $0.54 \mu\text{mol l}^{-1} \text{ h}$ when omeprazole was administered alone and $0.65 \mu\text{mol l}^{-1} \text{ h}$ when given after ranitidine (Table 1). The elimination half-life of omeprazole did not differ between the two experiments (0.58 vs 0.59 h).

Discussion

Ranitidine administration decreased the acidity in the stomach by approximately 5 log units. The goal of obtaining experimental conditions with a substantially decreased gastric acidity was thus fulfilled by this ranitidine dosing. The similar AUC values of omeprazole when given alone and after pretreatment with two doses of 300 mg ranitidine consequently indicate that gastric acidity has negligible effect on the bioavailability of omeprazole. By comparison, prior investigations with repeated omeprazole dosing in the same subjects resulted in an increased AUC from 0.57 to $1.02 \mu\text{mol l}^{-1} \text{ h}$ from the first to the last day of 1 week's treatment, i.e. an increase of 78% ($P < 0.003$).

A previous study with repeated dosing of omeprazole in the dose range 10 to 40 mg (as EC granules) resulted in a dose-dependent increase in the AUC (Andersson *et al.*, 1989) and the inhibition of gastric acid secretion was found to be dose-dependent (Lind *et al.*, 1983). Since omeprazole is an acid labile compound, these two observations made us suggest that a possible explanation of the increased AUCs previously obtained was an increased absorption as a consequence of increased stability of the granules and, hence, decreased acid degradation of omeprazole in the stomach resulting from decreased gastric acid secretion during repeated dosing of the drug (Andersson *et al.*, 1989, 1990). The results from the present study clearly show, however, that this explanation can be ruled out as a major contributing factor to the increased AUC during repeated dosing. Furthermore, concomitant administration of antacids and omeprazole did not result in an increased AUC of omeprazole which provides further support to our conclusion (Tuynman *et al.*, 1987). Thus, the alternative explanation, that a decreased hepatic metabolism of omeprazole might be responsible for the initial increase in AUC during repeated dosing (Andersson *et al.*, 1989, 1990) might instead be considered to be the more likely explanation. Since the elimination half-life of omeprazole was similar in the two experiments it is probably a decreased first-pass elimination that causes the increased AUC. Similar findings have been reported for other drugs, for instance metoprolol, which also displays an increase in AUC during repeated dosing (Jordö *et al.*, 1980).

The earlier attainment of the maximum plasma concentrations of omeprazole in the ranitidine experiment might be explained by a more rapid emptying of the stomach at the high pH values obtained (Hunt *et al.*, 1972). Alternatively, the omeprazole granules, which dissolve at pH values above 6.0, might have already

dissolved in the stomach and hence can be absorbed more rapidly.

It can be concluded that gastric acidity has negligible influence on the bioavailability (i.e. AUC) of omeprazole administered as EC granules.

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