Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules

H. A. R. E. TUYNMAN*, H. P. M. FESTEN†, K. RÖHSS‡ & S. G. M. MEUWISSEN

Department of Gastroenterology, Free University Hospital, Amsterdam, The Netherlands

Twelve male volunteers were studied after a single oral dose of 20 mg omeprazole given as enteric-coated granules with and without concomitant administration of 10 ml of a potent liquid antacid (buffering capacity 56.6 mmol 10 ml⁻¹) under fasting conditions. No statistically significant differences were detected in median $C_{\max}$ ($0.41 \approx 0.53 \mu\text{mol l}^{-1}$), the geometric mean AUC ($0.80 \approx 0.81 \mu\text{mol l}^{-1} \text{ h}$) or median $t_{\max}$ (1.25 h), with and without antacid.

Keywords antacids omeprazole interaction

Introduction

Omeprazole is a substituted benzimidazole that has a pronounced, dose-dependent and long-lasting inhibitory effect on basal and stimulated gastric acid secretion (Lind *et al.*, 1983). It exerts its effect by a non-competitive antagonism of the enzyme H^+ , K^+ -ATPase, the gastric proton pump, located in the secretory membrane of the parietal cell (Fellenius *et al.*, 1981).

The antisecretory effect of omeprazole is directly proportional to the area under the plasma drug concentration-time curve (AUC), but is not dependent upon the plasma drug concentration at any given time (Lind *et al.*, 1983).

Omeprazole is chemically degraded at low pH values, and it has been shown that concomitant administration of sodium bicarbonate is required for adequate absorption of omeprazole given as a suspension (Pillbrand *et al.*, 1985). An acid-resistant oral formulation has, therefore, been developed. This formulation consists of enteric-coated granules (EC-granules) dispensed in hard gelatine capsules. The enteric coating dissolves at pH > 6 when the granules reach the duodenum. Even with this formulation the area under the plasma drug concentration-time curve (AUC) varies considerably between subjects

and increases during repeated dosing (Howden *et al.*, 1984a,b; Prichard *et al.*, 1985). This increase in bioavailability is probably partly due to a decreased acid degradation as a result of an increased inhibition of gastric acid secretion (Prichard *et al.*, 1985).

We have investigated the possibility that concomitant administration of antacids might alter absorption of omeprazole from EC-granules.

Methods

Twelve healthy male volunteers were studied. Their mean age was 21.9 years (range 20–28 years) and their mean weight was 76 kg (range 68–86 kg). Prestudy physical examination, laboratory screen and electrocardiogram were normal in all subjects. All volunteers gave written informed consent and the study was approved by the Ethics Committee of the University Hospital.

The study consisted of two phases during which a single dose of 20 mg omeprazole was given orally as enteric-coated granules dispensed in a hard gelatine capsule, alone or immediately after a single oral dose of 10 ml Maalox TC ($\text{Mg}(\text{OH})_2$;

*Present address and address for correspondence: Department of Internal Medicine, Franciscus Hospital, Boerhaavelaan 25, 4708 AE Roosendaal, The Netherlands.

†Present addresses: Department of Internal Medicine, Groot Ziekengasthuis, 's-Hertogenbosch, The Netherlands and ‡AB Hässle, Sweden.

acid binding capacity $28.3 \text{ mmol } 5 \text{ ml}^{-1}$) under fasting conditions. The experiments were conducted in random order and separated by 2 weeks. The volunteers were not allowed to take any medicine or alcohol during the 2 days prior to and during each experiment and smoking was not allowed on the morning of and during each experiment.

The volunteers came to the laboratory at 08.30 h on each experiment day, having fasted since 22.00 h on the previous day. An indwelling cannula for drawing blood was inserted in a forearm vein and Maalox TC and omeprazole or omeprazole alone was administered orally. Blood samples for analysis of plasma omeprazole concentrations were collected in heparinised tubes before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h after drug administration. Standard meals were served at time 2.5, 6 and 10 h after drug administration.

The blood samples were 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 . The samples were analysed for omeprazole at the Department of Analytical Chemistry at AB Hässle using h.p.l.c. The limit of determination was 30 nmol l^{-1} with a relative standard deviation of less than 10–15% (Lagerström *et al.*, 1984).

The area under the plasma drug concentration-time curve (AUC) was calculated using the trapezoidal rule. This variable was assumed to be log normally distributed. A 95% confidence interval for the ratio between geometric means for the AUC with and without antacid was computed using the logarithmic transformation.

Any effect of concomitant administration of antacids on the bioavailability of omeprazole was evaluated with respect to this 95% confidence interval.

Results

There were no significant differences between AUC and C_{max} after oral administration of 20 mg omeprazole as EC-granules with and without Maalox TC (Figure 1).

The confidence interval for the ratio between the geometric means of AUC with and without antacids was 0.85–1.15.

Peak plasma concentrations of omeprazole occurred after a median time of 1.25 h in both experiments (Table 1).

Appreciable inter-individual variation in C_{max} and AUC was observed.

Omeprazole was well tolerated and no changes in laboratory values or adverse effects related to drug exposure were observed.

Figure 1 Area under the plasma drug concentration-time curve (AUC; a), peak plasma drug concentration (C_{max} ; b) after oral administration of 20 mg omeprazole EC with and without antacid to 12 volunteers.

Table 1 Area under the plasma drug concentration-time curve (AUC), peak plasma drug concentration ($C_{\max}$) and time to peak plasma drug concentration ($t_{\max}$) after oral administration of 20 mg omeprazole EC with and without antacid to 12 volunteers

	$C_{\max}$ ($\mu\text{mol l}^{-1}$)		$t_{\max}$ (h)	
	With	Without	With	Without
Median	0.41	0.53	1.25	1.25
Range	0.12–2.03	0.13–3.01	0.5–20	0.5–3.0
<hr/>				
	AUC ($\mu\text{mol l}^{-1} \text{ h}$)			
	With	Without		
Geometric mean	0.80 (A)	0.81 (B)		
95% confidence interval for geometric mean	0.44–1.42	0.45–1.46		
Range	0.34–7.37	0.24–8.58		
R (= A/B)	0.99			
95% confidence interval for R	0.82–1.19			

Discussion

We conclude that the concomitant administration of a liquid antacid with high binding capacity (Maalox TC) has no significant influence on the plasma concentration of omeprazole after a single oral dose of 20 mg given as EC-granules. The calculated 95% confidence interval for the expected change, measured as the ratio between

the geometric means of AUC with and without antacids, indicated that the change in AUC, if any, was not greater than 15%. In addition, concomitant antacid administration did not have a consistent influence on either $C_{\max}$ or $t_{\max}$.

Capsules of enteric coated omeprazole granules were supplied by Astra Pharmaceuticals, Sweden.

References

- Fellenius, E., Berglinde, T., Sachs, G., Olbe, L., Elander, B., Sjöstrand, S.-E. & Wallmark, B. (1981). Substituted benzimidazoles inhibit gastric acid secretion by blocking $\text{H}^+ + \text{K}^+$ -ATPase. *Nature*, **290**, 159–161.
- Howden, C. W., Forrest, J. A. H. & Reid, J. L. (1984a). Effects of single and repeated doses of omeprazole on gastric acid and pepsin secretion in man. *Gut*, **25**, 707–710.
- Howden, C. W., Meredith, P. A., Forrest, J. A. H. & Reid, J. L. (1984b). Oral pharmacokinetics of omeprazole. *Eur. J. clin. Pharmacol.*, **26**, 641–643.
- Lagerström, P. O. & Persson, B. A. (1984). Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. *J. Chromatogr.*, **309**, 347–356.
- Lind, T., Cederberg, C., Ekenveld, G., Haglund, U. & Olbe, L. (1983). Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut*, **24**, 270–276.
- Lind, T., Moore, M. & Olbe, L. (1987). Intravenous omeprazole: effect on 24-hour intragastric pH in duodenal ulcer patients. *Digestion* (in press).
- Pillbrand, Å. & Cederberg, C. (1985). Development of an oral formulation of omeprazole. *Scand. J. Gastroenterology*, Supplement 108, 113–120.
- Prichard, P. J., Yeomans, N. D., Mihaly, G. W., Brian Jones, D., Buckle, P. J., Smallwood, R. A. & Louis, W. J. (1985). Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. *Gastroenterology*, **88**, 64–69.

(Received 31 March 1987,
accepted 8 August 1987)