Antisecretory effect and oral pharmacokinetics following low dose omeprazole in man

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The effects of single and repeated doses of omeprazole 10 mg on gastric secretion were studied in a group of six healthy subjects. Single doses had no significant effect on basal or stimulated acid output. After 7 days of treatment, there was a 93.1% reduction in basal acid output ($P < 0.02$) and a 66.5% reduction in stimulated output ($P < 0.01$). Pepsin output was not affected. Systemic availability of omeprazole, as reflected in the AUC, increased significantly ($P < 0.05$) with repeated dosing. Low doses of omeprazole can produce substantial reductions in acid output after repeated dosing.

Keywords omeprazole gastric secretion pharmacokinetics

Introduction

Omeprazole is a potent inhibitor of gastric acid secretion in man (Lind *et al.*, 1983; Walt *et al.*, 1983). We have previously reported on the anti-secretory action of 30 and 60 mg in healthy subjects (Howden *et al.*, 1984a). Basal and plateau acid output (BAO, PAO) were reduced by 66% and 71.2% respectively following the first dose of 30 mg of omeprazole. The extent of inhibition increased to 99.8% and 98.4% respectively after 7 days of treatment. Single doses of 60 mg reduced BAO by 91.7%, and PAO by 95.3%. After 7 days of treatment with 60 mg daily, there was greater than 99% inhibition of BAO and PAO. The near maximal inhibition of acid production on chronic dosing with 30 mg daily may indicate changes in drug disposition with repeated dosing or result from a non-competitive action of $H^+/K^+-ATPase$ (Lind *et al.*, 1983; Howden *et al.*, 1984a). We have therefore examined the pharmacokinetics of omeprazole and its effect on gastric secretion using a lower dose, 10 mg, given for 7 days.

Methods

Six healthy male subjects (mean age 25 years; range 22–30) took part in the study which was approved by the Greater Glasgow Health Board, Northern District. Subjects took omeprazole 10 mg daily for 7 days. Studies of gastric secretion were performed on the first and seventh days of treatment, and results compared with those obtained from a placebo study carried out 1 week previously. Omeprazole was administered as capsules of enteric-coated granules; placebo capsules were identical in appearance, and subjects were unaware as to whether they were receiving drug or placebo. BAO was measured from 6 to 7 h from drug administration; PAO was measured from 7 to 8 h in response to pentagastrin $1.2 \mu g kg^{-1}$ according to methods previously described (Howden *et al.*, 1984a). Volume of gastric secretion was recorded and aliquots were taken for determination of pepsin content (Berstad, 1975).

On the days when omeprazole was given, blood samples were taken from an indwelling

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venous cannula at 30 min intervals for 8 h for determination of plasma omeprazole concentrations by a sensitive h.p.l.c. method as previously described (Howden *et al.*, 1984b). The peak plasma concentration ($C_{\max}$) and the time to peak concentration ($t_{\max}$) were recorded. The area under the plasma concentration–time curve from 0 to 8 h (AUC) was calculated for each subject by the linear trapezoidal rule.

Results

Basal and stimulated acid and pepsin output and volume of gastric secretion following placebo and first and seventh dose of omeprazole 10 mg appear in Table 1. A single dose of 10 mg of omeprazole produced no significant changes in basal or stimulated gastric acid secretion. However, after 7 days treatment, there was a mean reduction of 93.1% in BAO ($P < 0.02$) and of 66.5% in PAO ($P < 0.01$). Pepsin output was not significantly altered but there was a reduction of 26.7% in the volume of basal secretion ($P < 0.02$).

As has been observed previously (Howden *et al.*, 1984b) there were wide inter-individual differences in the pharmacokinetics of omeprazole. Results for $t_{\max}$, $C_{\max}$ and AUC following first and last doses of omeprazole appear in Table 2. There was no significant change in $t_{\max}$ with repeated dosing, but $C_{\max}$ increased in all subjects ($P < 0.05$) as did AUC ($P < 0.05$). The median AUC increased from 172 to 401 $\mu\text{g l}^{-1} \text{h}$.

Discussion

The results of this study with low dose omeprazole are consistent with previous findings (Lind *et al.*, 1983; Howden *et al.*, 1984a,b). We have again demonstrated an increase in antisecretory effect with repeated dosing, accompanied by a rise in the systemic availability of omeprazole as reflected by an increase in AUC in all subjects. As omeprazole is acid-labile (Lind *et al.*, 1983; Howden *et al.*, 1984a) it is probable that the fraction absorbed is increased when there is suppression of acid secretion. When 15 mg omeprazole was given for 5 days the 30% in-

Table 1 Acid and pepsin output and volume of gastric juice after placebo, and after the first dose and seventh dose of 10 mg omeprazole ($n = 6$; mean $\pm$ s.d.)

	Acid output (mmol h ⁻¹)	Basal Pepsin output (mg h ⁻¹)	Volume (ml h ⁻¹)	Acid output (mmol h ⁻¹)	Stimulated Pepsin output (mg h ⁻¹)	Volume (ml h ⁻¹)
Placebo	2.5 ± 1.6	17.3 ± 8.4	97 ± 15	23.3 ± 8.2	13.6 ± 4.7	241 ± 65
First dose	1.4 ± 1.3	17.1 ± 6.5	80 ± 39	23.1 ± 8.6	18.2 ± 5.0	261 ± 47
Seventh dose	0.2* ± 0.3	15.5 ± 5.4	71* ± 26	7.8** ± 6.7	17.3 ± 9.5	151 ± 52

* $P < 0.02$, ** $P < 0.01$, paired *t*-test.

Table 2 Pharmacokinetics of omeprazole after 10 mg orally

Subject	$t_{\max}$ (h)		$C_{\max}$ ($\mu\text{g l}^{-1}$)		AUC ($\mu\text{g l}^{-1} \text{h}$)	
	First dose	Seventh dose	First dose	Seventh dose	First dose	Seventh dose
1	5.5	2.0	93	263	156	628
2	3.5	0.5	154	410	428	515
3	3.0	1.5	58	68	166	190
4	2.0	1.0	65	116	178	360
5	1.0	1.0	98	99	218	255
6	5.0	1.0	81	203	159	443
Mean $\pm$ s.d.	3.3 $\pm$ 1.7	1.1 $\pm$ 0.6	92 $\pm$ 34	193 $\pm$ 128	218 $\pm$ 106	399 $\pm$ 164
	NS		$P < 0.05$		$P < 0.05$	

Wilcoxon matched pairs sign-rank test.

crease in AUC was not statistically significant (Lind *et al.*, 1983). In the present study and in our previous report (Howden *et al.*, 1984b) the AUC increased in all subjects after repeated dosing. This is due to enhanced absorption of the drug, which we have previously shown to be accompanied by an increase in the absorption rate constant.

We have confirmed that at low doses omeprazole does not affect pepsin secretion, indicating selectivity of action in suppressing acid output.

Early clinical trials of omeprazole in patients with duodenal ulcer (Gustavsson *et al.*, 1983; Meyrick-Thomas *et al.*, 1984) have shown im-

pressive results in healing rates. The optimum therapeutic dose of the drug remains to be established, and the question of a maintenance dose has yet to be addressed, but the results of this study demonstrate that doses as low as 10 mg daily produce substantial suppression of acid output after multiple dosing. It may be that an initial loading dose of 30 mg followed by maintenance therapy with 10 mg daily could give adequate control of gastric acid secretion in patients with peptic ulcer.

Capsules of omeprazole and placebo were supplied by the Astra Clinical Research Unit, Edinburgh, Scotland.

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