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Oral Pharmacokinetics of Omeprazole

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Summary. The pharmacokinetics of omeprazole were studied in a group of healthy male subjects after single and repeated oral doses of 30 and 60 mg. Absorption of omeprazole from its enteric-coated formulation was unpredictable. There was a highly significant increase in the area under the plasma concentration time curve (AUC) after repeated dosing. Omeprazole increases its own relative availability following repeated dosing. This may be due to inhibition of gastric acid secretion by omeprazole which is an acid-labile compound.

Key words: omeprazole; gastric acid secretion, pharmacokinetics

Omeprazole, a substituted benzimidazole, is a powerful inhibitor of gastric acid secretion in man. It acts by non-competitive inhibition of parietal cell H^+/K^+-ATPase [1]. Single doses produce a dose-dependent inhibition of gastric acid secretion [2, 3]. However, after 30 or 60 mg daily for seven days, there is almost total inhibition of acid secretion [2]. A single dose of omeprazole exerts an antisecretory effect for more than 24 h [3, 4] although this is not related to plasma concentrations of the drug, which has a short elimination half-life [5]. Omeprazole is partly inactivated by gastric acid so the formulation currently being used for clinical trials [6] consists of enteric-coated granules of the drug in a capsule form. We describe the pharmacokinetics of this preparation following single and repeated dosing.

Methods

Twelve male subjects gave informed written consent to the study which was approved by the Research and Ethical Committee of the Greater Glasgow Health Board, Northern District. Subjects were aged 19 to 34 years (mean 25 years). None had any past medical history of note or was on any other medication. All had a normal physical examination and normal renal and hepatic function on standard biochemical tests. Subjects were randomised to one of two groups taking either 30 or 60 mg of omeprazole/day as a single morning dose, for 7 days. Serial blood samples were collected following the first and seventh doses of omeprazole.

Blood samples were immediately transferred to a cooled heparinised tube and spun down in a refrigerated centrifuge. The supernatant plasma was transferred to a plain tube containing 20 µl of 1 M sodium carbonate. Plasma samples were stored at −20 °C until analysis.

Omeprazole concentration in plasma was determined using a reverse phase HPLC assay with UV detection.

Omeprazole and internal standard were extracted at pH 6.5–7.0 from plasma into methylene chloride. An aliquot of the extract was applied using an autosampler (Hewlett-Packard 1084 B) on to 250 × 4 mm spherisorb 5 ODS column. The drug and internal standard were chromatographed as ion pairs with pentane sulphonic acid and quantified by UV detection at 302 nm. The method is both sensitive and reproducible with a detection limit (arbitrarily defined as two times baseline noise) of 10 µg/ml and a coefficient of variation of 4.2% over the range 25 to 600 µg/l.

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 hours (AUC) was calculated for each subject by the trapezoidal rule. Differences between first and seventh doses were compared using Student's paired *t*-test. Using the mean plasma levels from each group, data were fitted to a one-compartment oral

Table 1. Pharmacokinetics of omeprazole after 30 mg or 60 mg orally

30 mg Subject	t_{max}		C_{max}		AUC	
	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7
1	1.0	1.5	223	239	338	496
2	1.5	4.5	690	610	937	1287
3	1.0	5.0	632	1000	1620	2830
4	3.0	2.0	305	489	748	1820
5	1.0	3.5	1160	1260	2270	3550
6	6.0	1.0	338	675	781	2130
60 mg Subject	t_{max}		C_{max}		AUC	
	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7
7	1.0	2.0	860	1710	2040	6610
8	1.0	7.0	2070	1860	3120	5410
9	5.0	1.0	3830	2270	5000	7070
10	4.5	5.5	993	1310	2300	3230
11	1.0	0.5	974	2110	1380	5700
12	2.5	2.5	1270	3180	4440	7850

pharmacokinetic model. The parameters of absorption rate constant (k_a), elimination rate constant (k_{el}), extrapolated peak plasma level (A) and time lag for absorption (t_{lag}) were derived. Elimination half-life ($t_{½}$) was calculated from the equation $t_{½} = \frac{0.693}{k_{el}}$.

Results

The absorption of omeprazole was variable and unpredictable. Following a single dose of 30 mg, 4 out of 6 subjects attained maximum plasma concentrations within 1.5 h. Peak plasma levels varied from 223 to 1160 µg/l (mean 558), and AUC varied from 388 to 2270 µg h/l (mean 1123 µg h/l). After computer fitting of the data, values of 600 µg/l, 0.8 h^{-1}, 0.32 h^{-1} and 0.37 h were derived for A, k_a, k_{el} and t_{lag}) respectively (Table 1). After the seventh dose of 30 mg, the time to peak levels was delayed. Only 2 subjects attained peak levels within 1.5 h. C_{max} ranged from 239 to 1260 µg/l (mean 712 µg/l), and AUC ranged from 496 to 3550 µg h/l (mean 2019 µg h/l). There was a consistent and highly significant rise in AUC with repeated dosing ($p < 0.01$), the mean increase being 86%. After fitting the data, values for A, k_a, k_{el} and t_{lag} were 438 µg/l, 30.7 h^{-1}, 0.4 h^{-1} and 0.79 h respectively (Table 1). Elimination half-life was 2.17 h after a single dose and 1.73 h after repeated dosing.

After a single dose of 60 mg, 3 subjects attained C_{max} within 1.5 h. C_{max} ranged from 860 to 3830 µg/l (mean 1670 µg/l) and AUC varied from 1380 to 5000 µg h/l (mean 3050 µg h/l). When this data was fitted, values for A, k_a, k_{el} and t_{lag} were 2550 µg/l, 0.36 h^{-1}, 0.25 h^{-1} and 0.41 h respectively (Table 1). On repeated dosing, absorption remained unpredictable. Only one subject reached C_{max} within 1.5 h, and one was delayed until 7 h after dosing. C_{max} ranged from 1310 to 3180 µg/l (mean 2070), and AUC ranged from 3230 to 7850 µg h/l (mean 5980 µg h/l). There was a consistent and significant ($p < 0.01$), rise in AUC with repeated dosing. Mean rise in AUC was 128%. When this data was fitted, values for A, k_a, k_{el} and t_{lag} were 1620 µg/l, 7.06 h^{-1}, 0.21 h^{-1} and 0.85 h respectively (Table 1). Elimination half-life was 2.77 h after a single dose and 3.30 h after repeated dosing.

Discussion

We have previously shown [2] that the degree of inhibition of gastric acid secretion by omeprazole increases with repeated dosing. It has also been shown [3, 4] that a single dose of omeprazole exerts an effect for longer than 24 h. This is not related to accumulation of the drug in plasma, as we did not detect any omeprazole in blood taken from subjects 24 h after a dose. Continuing antisecretory effect does not depend on sustained plasma concentrations of the drug.

The results of our present study show that omeprazole increases its own oral availability with re-

peated dosing. We have demonstrated a significant increase in AUC with repeated dosing. AUC increased in all 12 subjects. The elimination half-life did not significantly change, but there was a marked increase in the absorption rate constant suggesting that the increased availability is secondary to enhanced absorption of the drug. It is known that omeprazole is partly destroyed by gastric acid [5], so it is perhaps not surprising that absorption is more complete when acid secretion is reduced.

In the preparation used, omeprazole has somewhat unpredictable absorption. However it appears that the drug is well absorbed and that absorption increases with repeated dosing, possibly related to inhibition of gastric acid secretion.

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