Digestion *34:* 78–86 (1986)

0012–2823/86/0342–0078$2.75/0

Intravenous Omeprazole: Effect on 24-Hour Intragastric pH in Duodenal Ulcer Patients[1]

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Key Words. Omeprazole · Intragastric pH · Duodenal ulcer patients

Abstract. This study was aimed to identify an intravenous dosage regime of omeprazole which would sufficiently suppress acid secretion to maintain intragastric pH > 4 continuously. Thirteen duodenal ulcer patients in remission received omeprazole in daily intravenous doses ranging from 40 to 200 mg. Doses were successively increased as dictated by patient response. The intragastric pH data indicated that omeprazole given in twice or thrice daily regimes in total intravenous amounts of 200, 160 and 160 mg over a consecutive 3-day period markedly inhibited acid secretion and maintained intragastric pH > 4 with few and short-term exceptions.

Indications for the use of intravenous gastric antisecretory agents have included such conditions as acute upper gastro-intestinal (GI) bleeding, prophylaxis of stress-induced GI haemorrhage, gastric retention on an ulcer basis and prophylaxis to the pulmonary acid aspiration syndrome in anaesthetized patients [1–5]. In vitro studies have shown the harmful effect of gastric acid on blood coagulation and platelet aggregation [6]. Consequently, treatment of upper GI bleeding has been suggested to include either a complete inhibition of acid secretion or total neutralization of secreted acid [7]. The H_2-receptor antagonists have been shown to substantially increase intragastric pH in healthy subjects [8] but the reports on their effectiveness in patients who are critically ill are conflicting [9–13]. Moreover, no controlled trial of sufficient magnitude has shown convincing evidence in favour of H_2-receptor antagonist therapy in patients with upper GI bleeding [14].

[1] Sponsored by grants from the Swedish Medical Research Council (project No. 17X–760).

Omeprazole, classified as a gastric proton pump inhibitor, is a substituted benzimidazole which inhibits gastric acid secretion via a selective and noncompetitive antagonism of the H^+/K^+-ATPase enzyme in the parietal cell secretory membrane [15]. Omeprazole, when administered orally, has been shown to reduce gastric acidity to a greater extent than H_2-receptor antagonists [16] and to be effective clinically [17, 18]. The acid inhibitory potency and the long duration of action of omeprazole have indicated that it might have some value in the treatment of upper GI bleeding.

This study was designed to identify an appropriate intravenous dosage regime for omeprazole, sufficient to keep intragastric pH above 4 in duodenal ulcer (DU) patients for a 3-day period. The selected dosage regime should be easily applied in therapeutic practice and should be used in future clinical studies of acute upper GI bleeding. No pH data in DU patients in remission are available for the H_2-receptor antagonists. In vitro studies have shown the profound effect of a pH gradient on blood coagulation and platelet aggregation and indicated that an elevation of intragastric pH would be beneficial in preventing clot digestion and controlling GI bleeding [6]. The minimum criterion of a successful dosage regime in the present study was defined as being suppression of acid secretion sufficient to maintain intragastric pH above 4 over the investigation period.

Patients, Materials, Methods

The study was approved by the Ethical Committee of the Medical Faculty, University of Gothenburg, and written informed consent was obtained from all patients prior to participation.

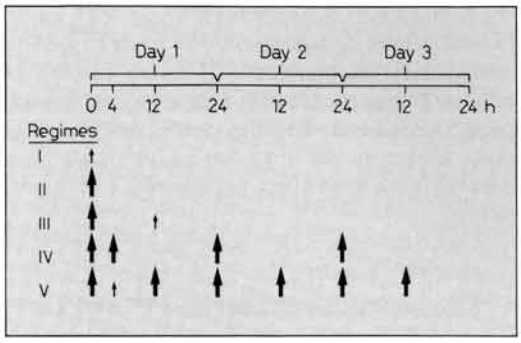

Fig. 1. Study design depicting dosage regimes for intravenous omeprazole. The thin arrows indicate 40 mg omeprazole; the thick arrows indicate 80 mg omeprazole. Dosage regimes I–III represent 1-day dosing; dosage regimes IV–V represent multiple-day dosing.

Patients

Thirteen outpatients (including 1 woman) with a mean age of 52 years (range 29–66), a mean weight of 75 kg (range 66–100) and a mean height of 175 cm (range 162–191) paritcipated in the study. All patients had an endoscopically verified history of DU disease, in no case from ulcerogenic medication, and all were considered healthy at the physical examination prior to the study.

Study Design and Dosage Regimes

This study consisted of a series of 24-hour recordings of intragastric pH in patients receiving various intravenous doses of omeprazole over 1- to 3-day periods. The study was divided into two parts. The first part (dosage regimes I, II and III) consisted of 1-day dosing and successively increasing doses were investigated. The second part, regimes IV and V, was multiple-day dosing; omeprazole was administered over a 3-day period and the patients were studied during the first and last 24-hour period. A full description of the dosage regimes is given in figure 1. Only those dosage regimes which would be practical and convenient to administer in a clinical situation were evaluated.

The dosage regime selection was based upon patients' response. In those patients whose response at a certain dose level failed to meet the predefined crite-

rion of study success, i.e., intragastric pH > 4 over the 24-hour period, the subsequent dose was increased. In those patients exhibiting adequate intragastric control at a low dosage level, a higher dose was not investigated. Two patients who failed to meet the criterion of study success in the first part of the study were included in the second part, together with 6 additional patients.

Drug Formulation

The intravenous omeprazole formulation was available as a freeze-dried compound/polyethylene solvent combination and contained omeprazole 4 mg/ml.

Intragastric pH Assessments

A double-lumen nasogastric tube (Salem tube 14 CH) was placed under fluoroscopic control with its tip in the most distal part of the stomach of the patients, who had fasted overnight. The stomach content was emptied. Samples of gastric content (2–5 ml) for recording of intragastric pH by a standard pH meter (Radiometer, Copenhagen) were aspirated 4 times of 15-min intervals during a pre-dose assessment. Gastric samples were not replaced. The first dose of omeprazole was then given as a bolus injection at a constant rate over 10 min. Gastric samples for the recording of intragastric pH were similarly taken at frequent intervals (10–30 min) for 120 min following the first omeprazole dose, then every hour for the next 24 h. For dosage regimes IV and V, which included dosing for a further 2 days, intragastric pH was additionally recorded at 1-hour intervals from 20–24 h and from 0–20 h on the 2nd and 3rd days, respectively. Eleven of the patients also underwent a 24-hour assessment of basal intragastric pH (consisting of hourly determinations) in which no omeprazole was given. This assessment was performed at least 30 days after the last dose of omeprazole and provided baseline data for comparative purposes. Two patients were lost to basal recordings due to subsequent, elective vagotomy. Patients remained fasting during all intragastric pH recordings but received intravenous glucose supplementation (2.5 l 10% glucose/24 h). Smoking was allowed throughout the study.

Drug Disposition Assessments

Blood samples (5 ml) for assay of plasma omeprazole concentration were generally taken before and 0, 2, 5, 7, 10, 15, 20, 25, 30, 35, 45, 65, 95, 125, 185, 305, 425 and 600 min after the first and last omeprazole doses in any dosage regime. For patients receiving dosage regime V, blood samples were taken only in those patients where previous, pharmacokinetic omeprazole data were unavailable. The plasma concentration of omeprazole was analysed using high-pressure liquid chromatography.

Evaluation of Safety

A full laboratory screen (including haematology, blood chemistry and urine analysis) was taken prior to omeprazole dosing, during washout periods and on the 5th day after each dosage regime. All patients were asked to report any symptoms or side-effects of which they became aware.

Calculations and Statistics

Intragastric Acidity. In each sample of gastric juice, pH was measured and converted to hydrogen ion activity (H^+, mmol/l) by use of the equation:

$$[H^+] = \frac{1}{\text{antilog pH}} \cdot 1{,}000.$$

The total intragastric acidity produced on the 1st day by each intravenous dosage regime was taken to be the area under the $[H^+]$ time curve from 1 to 24 h post commencement of dosing. Intragastric acidity calculated during the 1st h post dosing was not included in this determination since such values were considered to partly represent residual acid produced during the pre-dose assessment. Intragastric acidity produced on the 2nd and 3rd day of dosing (for regimes IV and V) was similarly estimated as the area under the $[H^+]$ time curve from time 20 h on day 2 to time 20 h on day 3. All areas were calculated using the trapezoidal rule [19]. The reduction in total intragastric acidity following each dosage regime was calculated for each patient as percentage change from the basal assessment recording.

Intragastric pH data were used to construct the graph of the percentage of hourly pH readings falling below 4 from 1 to 24 h on the 1st day of each intravenous dosage regime. In the determinations of mean intragastric acidity and pH data, hourly intragastric acidity calculations have been used. Statistical comparisons of total intragastric acidity were made between dosage regimes IV and V and basal assessment using the Student t test. Dosage regimes I, II and III comprised too few patients to allow statistical comparisons.

Drug Disposition. Parameters of drug disposition were calculated from plasma concentration data determined after each intravenous omeprazole dose. The apparent elimination half-life ($t_{½}$ β) was determined after regression analysis of the linear terminal phase (from 95 min onwards) of the log concentration-time profile. Total area under the concentration-time curve (AUC, μmol·h/l) was calculated using the trapezoidal rule [19] and adding the usual 'area to infinity' correction.

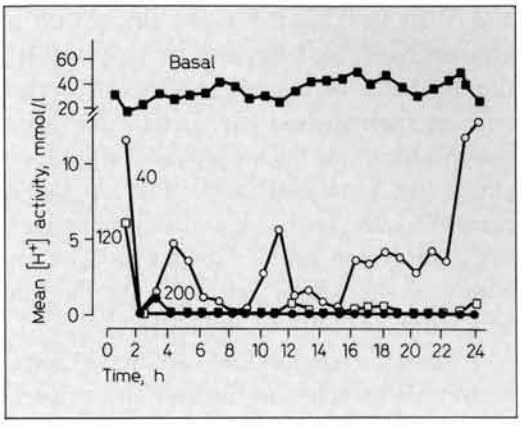

Fig. 2. Mean intragastric acidity-time profile determined during the basal assessment (■) and for 1–24 h following administration of intravenous omeprazole dosage regimes. Figures correspond to given dose (mg) of omeprazole. ○ = 40 mg (dosage regime I); □ = 120 mg (dosage regime III); ● = 200 mg (dosage regime V).

Results

The data from this study have been assessed both in terms of incidence of pH value falling below the predefined value of 4 and in terms of total intragastric acidity.

Intragastric Acidity

Summarized data of the total [H+] activity following the various dosage regimes, the percentage reduction in [H+] activity compared to the basal assessment and pharmacokinetic parameters are displayed in table I. The effect of the intravenous omeprazole dosage regimes I, III, and V on the mean intragastric acidity-time profiles over the first 24 h as compared to placebo is displayed in figure 2.

A marked reduction in intragastric acidity was observed in all patients following all intravenous omeprazole dosage regimes (table I). This effect was rapid in onset and a decreased acidity was observed in all patients within 1 h of the start of the first dose of omeprazole. Omeprazole in total daily doses of 40, 80 and 120 mg in the 1-day dosing part, regimes I, II, and III, suppressed intragastric acidity by 89, 98 and 99%, respectively. The finding of the two multiple-day dosage regimes IV and V also indicated a continuously high reduction in intragastric acidity despite a lower dose on the 2nd and 3rd day (table I). Compared to the basal recording, the reduction in intragastric acidity preduced by dosage regimes IV and V was statistically significant ($p < 0.001$).

Intragastric pH

The percentage of hourly recordings which fell below the pH level of 4 during the study period for each patient following each intravenous dosage regime is presented in table II. Similarly the mean percentages of hourly recordings of pH falling below values ranging from 1 to 8 are depicted for all patients in regimes I, III, and V in figure 3.

The incidence of intragastric pH values falling below 4 was markedly reduced following each intravenous dosage regime (table II) and, compared to the basal assessment, was statistically significant for dosage regimes IV

and V ($p < 0.001$). For the first group of patients receiving 1-day dosage regimes I–III, the incidence of low pH readings decreased with increasing dose (fig. 3, table II). Most patients receiving the multiple-day dosage regimes (fig. 3, table II) were not completely controlled on the 1st day after omeprazole, but a pH value above 4 could be achieved with one short-term exception on the 2nd and 3rd days of dosing (table II).

A large inter-individual variation in intragastric pH response to intravenous omeprazole was observed (table II) and the dose required to control intragastric pH to above 4 during the first 24-hour period ranged from 40 to 200 mg among the 13 patients. Among those patients receiving single-day dosage regimes only 1 (patient 04, table II) maintained intragastric pH above 4 following 40 mg (regime I) while 5 out of 7 patients displayed adequate intragastric pH control following doses up to 120 mg (regime I–III, table II). The 2 remaining uncontrolled patients from this group were included with the newly recruited patients in the assessment of the multiple-day dosage regimes. Seven out of 13

Table I. Summary of intragastric acidity, and percentage reduction with respect to basal recording, and pharmacokinetic parameters following intravenous omeprazole dosing

Dosage regime	Patients n	Total intragastric acidity, mmol·h/l			AUC µmol·h/l mean ± SEM	$t_{½}$ β mean
		basal mean ± SEM	post-dose mean ± SEM	percent reduction		
I	4	842 ± 10 (817–870)	91 ± 33 (48–203)	89.0 (75.6–94.5)	14.3 ± 4.6 (5.7–29.9)	1.43 (0.9–2.0)
II	5	878 ± 38 (817–1,025)	21 ± 9 (8–57)	97.6 (93.0–99.0)	23.5 ± 4.6 (13.5–33.3)	1.51 (1.1–1.9)
III	5	878 ± 38 (817–1,025)	7 ± 1 (4–10)	99.2 (98.8–99.6)	39.5 ± 4.9 (25.2–48.0)	1.40 (0.6–2.2)
IV	6	998 ± 180 (496–1,727)	42 ± 26 (3–164) day 1	96.7 (90.5–99.5) day 1	31.4 ± 6.0 (16.5–56.8)	1.27 (0.8–2.0)
			21 ± 8 (0–54) day 2/3	98.0 (95.0–100) day 2/3		
V	6	911 ± 221 (225–1,727)	20 ± 8 (0–49) day 1	97.5 (90.0–100.0) day 1	26.7 ± 7 (9.1–53.3)	1.46 (0.8–2.7)
			0 ± 0 (0–0.2) day 2/3	100 (100) day 2/3		

Figures in parentheses are ranges.

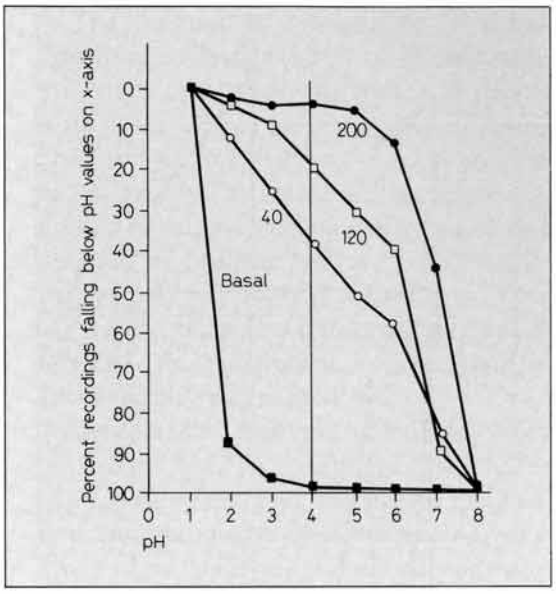

Fig. 3. Percentage of hourly pH recordings falling below values ranging from 1 to 8 during the basal recording (■) and following regimes I, II and V recorded during the first 24-hour period. Figures correspond to given dose (mg) of omeprazole. ○ = 40 mg (dosage regimes I); □ = 120 mg (dosage regime III); ● = 200 mg (dosage regime V).

Table II. Percentage of hourly recordings below pH 4 during a 24-hour study period following various dosage regimes of intravenous omeprazole

Patient No.	Basal	I	II	III	IV		V		$t_{½}$ β mean
					day 1	day 2/3	day 1	day 2/3	
01	100	22	9	0	–	–	–	–	1.90
02	96	87	39	13	26	0	–	–	1.12
03	100	35	17	0	–	–	–	–	1.81
04	–	0	–	–	–	–	–	–	2.04
05	100	48	26	9	0	22	0	0	1.05
06	100	–	4	0	–	–	–	–	1.40
07	–	–	–	0	–	–	–	–	1.48
08	100	–	–	–	39	37	13	0	1.03
09	100	–	–	–	35	33	4	0	1.27
10	92	–	–	–	39	19	17	4[1]	0.80
11	96	–	–	–	17	0	–	–	1.98
12	92	–	–	–	–	–	0	0	1.62
13	100	–	–	–	–	–	4	0	2.70
Mean	98	38	16	4	26	19	6	0.7	

Individual mean values of omeprazole plasma half-life ($t_{½}$ β) are also displayed.

[1] Represents a single hourly period of pH below 4 (3.96).

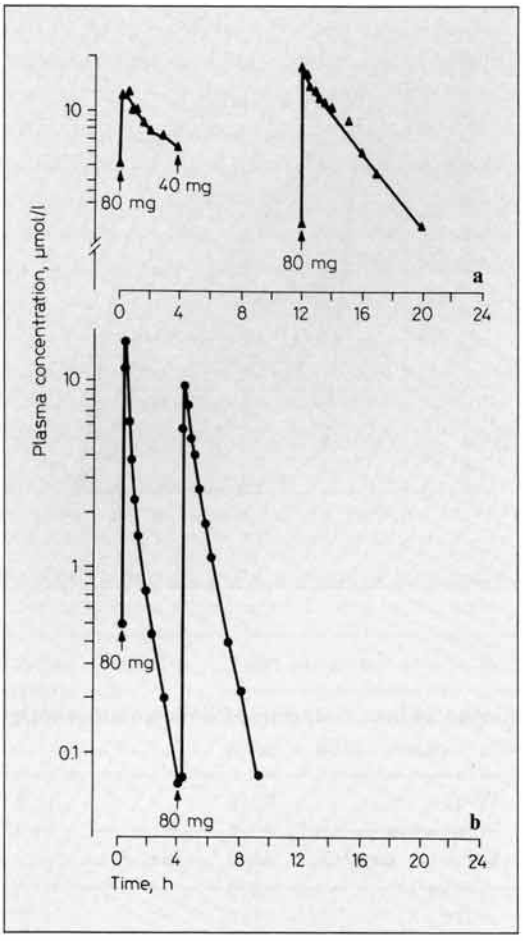

Fig. 4. Plasma concentration-time profiles determined following repeated intravenous omeprazole dosing. **a** Data from patient 13 indicate slow elimination (day 1 of regime V). **b** Data from patient 10 indicate rapid elimination (day 1 of regime IV).

patients were controlled on the 1st day following doses up to 200 mg (regime I–V). Of these patients receiving multiple-day dosing, a further 5 achieved intragastric pH control during days 2 and 3 while the 6th patient showed one pH value slightly below 4 (3.96) but was otherwise controlled (table II).

Drug Disposition

Mean data of $t_{½}$ β and AUC are presented in table I and individual values of $t_{½}$ β in table II. Representative plasma concentration-time profiles are displayed in figure 4. An approximate 3-fold variation in $t_{½}$ β was observed between participating patients, although data for any given patient indicated that $t_{½}$ β remained relatively constant, irrespective of dose. A proportional increase in AUC was observed with increasing dose and similar inter-individual variability in this parameter was observed.

Evaluation of Safety

With the exception in 1 patient experiencing faintness and bradycardia on one occasion following an 80-mg dose, intravenous omeprazole was well tolerated. These symptoms were ascribed to a vagal reaction. Variation in laboratory values outside the normal laboratory range were few and occurred both before and after drug administration.

Discussion

This study was designed to identify an appropriate intravenous dosage regime for omeprazole sufficient to keep intragastric pH above 4 in DU patients and to be tested in future clinical studies of acute upper GI bleeding. The primary objective of the present study was to select a dosage regime appropriate for 3 days' omeprazole therapy which would be both convenient to administer and would maximally inhibit intragastric acidity to the predefined extent in the investigated patients. The findings of this study indicated that the intravenous administration of omeprazole to DU patients in daily

doses ranging from 40 to 200 mg produced a profound suppression of acidity and with the highest omeprazole dose intragastric acidity was almost abolished and the intragastric pH was at least elevated above 4.

The patient group were all DU patients known to exhibit hypersecretion of gastric acid [20]. They were thus considered an appropriate model for patients with upper GI bleeding. The clinical management of patients with such bleeding often entails withholding food until bleeding ceases. The intragastric acidity determinations in this study were consequently performed in patients in a representative fasting state, which also reflects a more aggressive intragastric milieu than commonly exists in most pH-profile studies where the intake of buffering food is permitted.

Consideration of the intragastric acidity data from the present study indicated that a high degree of inhibition was obtained at all dosage levels (mean percent reduction on day 1 of 89, 98, 99, 97 and 98 at 40, 80, 120, 160 and 200 mg, respectively). The persistent production of the small amounts of acid at intravenous doses of 120 mg and above would indicate that it is difficult with a conventional dosage regime to totally inhibit acidity in all individuals on the 1st day of dosing, despite giving high intravenous doses. It has been documented earlier that the inhibitory effect of omeprazole is enhanced on repeated daily oral dosing [15]. The findings of the multiple-day dosage regimes IV and V (table I) also support this conclusion. In both cases, intragastric acidity was lower on the 2nd and 3rd day of dosing, even though a lower total dosage was administered. It seems likely, therefore, that total inhibition of intragastric acidity is possible on repeated intravenous dosing.

The variation in dose required to maintain intragastric pH above 4 in the patients in this study was relatively large and ranged from 40 to 200 mg on the 1st day of dosing and from 80 to 160 mg on the 2nd and 3rd day of dosing. The higher dosage regime was needed to achieve adequate pH control in a majority of patients. However, in most patients with a pH above 4 following any dosage regime, the actual intragastric pH was in fact 6–7 (fig. 3), implying a suppression of gastric acidity by about 99.9%.

Omeprazole disposition derived from $t_{1/2}$ β and AUC is consistent with linear pharmacokinetics and an earlier observation that variation exists between individuals in their ability to metabolize omeprazole (tables I, II). In previous investigations on oral omeprazole, AUC and inhibitory effect on acid secretion were shown to be significantly correlated [15]. Similarly, in this study, the 2 patients in the 1-day dosing group (patients 02 and 05) demonstrating the poorest response of intragastric pH to omeprazole also exhibited the most rapid systemic elimination of omeprazole as suggested by low values for $t_{1/2}$ β (table II) and AUC. The apparently poorer response to intravenous omeprazole of the multiple-day dosing group of patients as compared to the first, can be explained by the selection of patients with rapid elimination character.

In summary, the results indicate that omeprazole given in total intravenous doses of 200, 160 and 160 mg over a consecutive 3-day period very markedly inhibited intragastric acidity and maintained intragastric pH above 4 in almost all patients over the experimental period. This dosage scheme of omeprazole should be tested in the treatment of bleeding peptic ulcers.

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Received: August 29, 1984
Received in revised form: May 15, 1985

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