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Effect of Intravenous and Oral Omeprazole on 24-Hour Intragastric Acidity in Duodenal Ulcer Patients

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Nine patients with duodenal ulcer were on separate occasions given omeprazole, 20 mg orally, 10 mg intravenously (IV), and 40 mg IV once daily for 5 days. On day 1, the median reduction of 24-hour intragastric acidity was 42.2% for the 20-mg oral dose and 54.8% and 88.4% for the two IV doses, respectively, but the between-patient variability was considerable for all three doses. On day 5, the degree of reduction had increased for all three doses to a median value of 99.9% for the 20-mg oral dose and 95.7% and 99.9% for the two IV doses, respectively. Plasma omeprazole concentrations increased significantly from day 1 to day 5 only for the 20-mg oral and 40-mg IV doses. Thus, the increased pharmacological effect of omeprazole during repeated once daily administration can only partly be explained by increased plasma concentrations, suggesting that some additional factor(s) must influence the degree of reduction of 24-hour intragastric acidity. Thus, when determining the optimal dose of omeprazole for acid inhibition, the route and duration of administration must be taken into consideration; after 5 days of once-daily administration of doses as low as 10 mg IV and 20 mg orally are effective and dependable in reducing 24-hour intragastric acidity in patients with duodenal ulcer. However, a daily dose of 40 mg IV omeprazole is not sufficient to keep intragastric pH above 4 in all patients during the first day of treatment.

Omeprazole inhibits gastric acid secretion via a selective antagonism of the gastric proton pump [H^+,K^+-adenosine triphosphatase (ATPase)] in the parietal cell secretory membrane. For unconscious patients or patients who for other reasons are unable to take medication orally (PO), it is necessary to inhibit acid secretion via the intravenous (IV) route of administration. Single IV doses ranging from 10 to 80 mg cause a dose-dependent and long-lasting inhibition of pentagastrin-stimulated gastric acid secretion in healthy subjects, with increased antisecretory effect after repeated once daily administration.[1] Single doses of IV omeprazole increase intragastric pH in patients with duodenal ulcer but has been reported to be less effective than PO dosing.[2,3] However, single IV and multiple PO doses were often used. There is an accumulative effect after repeated dosing,[4] and there remains the possibility that the potency and consistency of acid inhibition after IV dosing are enhanced by multiple dosing.

Thus, the present study was performed to compare the effect of the recommended PO dose for healing of peptic ulcer (20 mg) with a bioequivalent IV dose (10 mg) and the single IV dose considered to be optimal for inhibition of pentagastrin-stimulated gastric acid secretion (40 mg) on 24-hour intragastric acidity in patients with duodenal ulcer disease in symptomatic remission.

Patients and Methods

Patients

Nine patients, seven male and two female, with a mean age of 37 years (range, 26–63) were included and completed the study. The patients had a past history of duodenal ulcer disease with at least one episode of recurrent ulcer symptoms within the previous 36 months. The patients were currently in symptomatic remission; none were on maintenance treatment. Endoscopy, to exclude a silent ulceration, was not performed. The patients' median basal acid output was 0.6 mmol/h and median peak acid output to pentagastrin (6 μg/kg) 24.8 mmol/h. The patients were otherwise considered healthy at their pretreatment evaluation.

Informed written consent was obtained, and the study was conducted according to the Declaration of Helsinki as revised in Tokyo, Japan, 1975. Review and approval of the

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study was obtained from the Ethics Review Committee of the Faculty of Medicine at the University of Alberta.

Study Drugs

The IV formulation of omeprazole consisted of 40 mg lyophilized omeprazole as sodium salt and 10 mL solvent (40% polyethylene glycol 400; NaH_2PO_4, 1.3 mg/mL; and Na_2HPO_4, 0.3 mg/mL) in a twin-ampule combination package. Immediately before use, the solvent was added to the omeprazole ampule and thoroughly mixed. Omeprazole, 10 mg (2.5 mL) and 40 mg (10 mL), was given as intermittent (every 30 seconds) IV injections over 5 minutes.

PO omeprazole was given as one hard gelatine capsule containing 20 mg omeprazole as enteric-coated granules. The capsule was taken in the morning before breakfast with a glass of water.

Study Procedures

Within 14 days of inclusion each patient had a baseline 24-hour acidity test using an aspiration technique without the use of antisecretory medication. Each patient then took part in three study periods of 5 days each, which were separated by a washout period of at least 9 days. In each study period omeprazole, 10 mg IV, 40 mg IV, or 20 mg PO, was given once daily in the morning. The order of treatments was randomized. On day 1 in each study period, the patient came to the Clinical Investigation Unit in the morning, having fasted overnight and not taken any antacids from midnight. A nasogastric tube (14F) was passed and positioned in the most distal part of the stomach. The position was checked by a water recovery test. At 8 AM a sample (5 mL) of gastric juice was aspirated, after which omeprazole, 10 mg IV, 40 mg IV, or 20 mg PO, was given according to the patient randomization. From 9 AM until 8 AM the next morning, hourly samples of gastric juice were aspirated. In each sample, pH was recorded to the nearest 0.01 unit using a combined glass and reference electrode and a pH meter (Radiometer, Copenhagen). The electrode was calibrated using standard buffers of pH 2.01, 4.03, and 7.00 both before and after the study. During the study day, serial blood samples were taken through an indwelling cannula in heparinized tubes and plasma omeprazole concentrations determined by high-performance liquid chromatography.[5] Standardized meals were served at 8:30 AM, 12:30 PM, and 6:30 PM. Each meal was consumed over 15 minutes. Food, liquids, and cigarette consumption were carefully recorded during the baseline acidity test. This schedule was adhered to during all subsequent 24-hour tests.

On days 2–4, the oral medication was taken by the patient at home as instructed. The IV medication was given each morning at 8 AM at the Clinical Investigation Unit. On day 5 the intragastric acidity test was repeated, during which the fifth dose of omeprazole was given. Blood samples for omeprazole determination were taken as on day 1. Blood samples for a laboratory screen were also taken at the end of the experiment.

Calculations and Statistics

Intragastric acidity (i.e., hydrogen ion activity) was calculated as 10^{-pH} and expressed as mmol/l equivalents. The integrated 24-hour intragastric acidity was calculated as the area under the acidity-time curve using the trapezoidal formula and expressed as mmol · h L^{-1}. The area under the plasma omeprazole concentration-time curve (AUC) was also calculated using the trapezoidal formula. For the IV doses, the AUC was extrapolated to infinity by adding the residual area calculated as the last measured plasma concentration divided by the elimination rate constant (β). This rate constant was determined by log-linear regression of the terminal slope of the plasma concentration curve. Pharmacokinetic parameters for the IV experiments were calculated as follows: $t_{1/2} = 0.693/\beta$; systemic clearance (CL) = dose/AUC; and volume of distribution at steady state (V_{SS}) = AUMC × CL/AUC, where *AUMC* is the area under the first moment curve.[6] The bioavailability (f) of the PO 20-mg dose was calculated using the AUC for the corresponding 10 mg IV dose multiplied by 2. Statistical comparisons were made using Wilcoxon matched pairs signed rank test with a *P* value of ≤ 0.05 regarded as significant.

The relationship between percent reduction of integrated intragastric acidity and plasma omeprazole AUC was evaluated using linear regression analysis after logit transformation where $x = \log_{10}$ AUC and y = ln %reduction/(100 − %reduction).[7]

Results

Intragastric Acidity

The median 24-hour profiles for intragastric pH are shown in Figure 1 and the cumulative relative pH-frequency profiles in Figure 2. During the first day of treatment all three doses caused a statistically significant reduction of pretreatment integrated intragastric acidity, but the response in the individual patients was variable (Table 1). After 5 days of once daily dosing there was a significant reduction in intragastric acidity in all patients on all doses (Table 1).

The percentage of time with an intragastric pH > 4 and >7 are shown in Table 1. In the pretreatment experiment intragastric pH was above 4 for <20% of the time in most patients. After a single IV dose of either 10 or 40 mg, the frequency of pH values <4 was increased in the majority of patients, but only one patient on each dose had a pH > 4 for the entire 24-hour period (Figure 3). After 5 days of dosing, the frequency of pH values >4 was significantly ($P = 0.0064$) increased for both doses. Despite this only one patient on the 10-mg dose could be maintained on a pH > 4 throughout the 24-hour period, whereas six of the nine patients could be maintained above this level with the 40-mg IV dose (Figure 3). No single

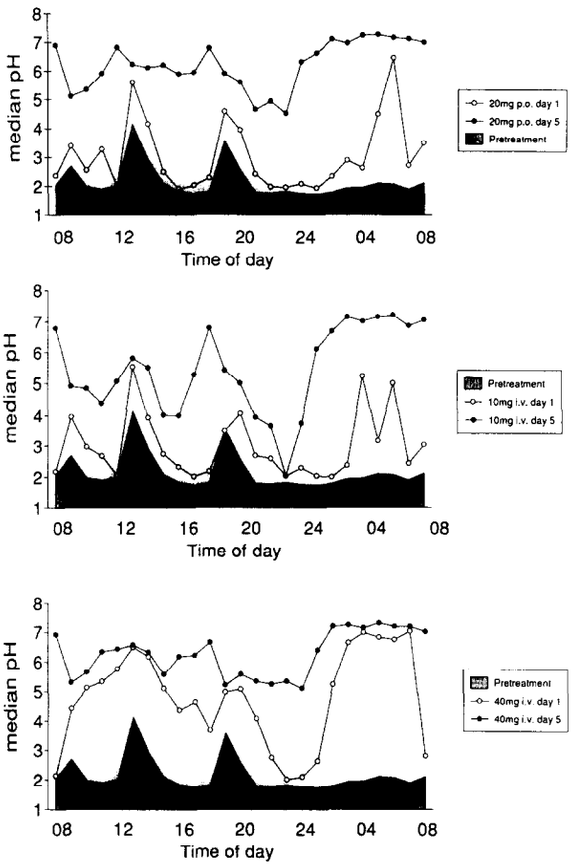

Figure 1. Median intragastric pH profile before and after the first and fifth once daily morning dose of omeprazole, 20 mg PO, 10 mg IV, and 40 mg IV. The dose was given at 9 AM.

patient had an unremitting anacidity (pH > 7) on any of the doses tested (Table 1).

Pharmacokinetics

The mean plasma omeprazole concentration-time curves are shown in Figure 4. After the first dose, the plasma omeprazole AUC was similar for the 10-mg IV and 20-mg PO doses but fourfold higher after the first 40-mg IV dose (Table 2). Both the plasma elimination half-life and clearance of omeprazole were similar for the two IV doses, suggesting linear kinetics in this dose range (Table 2). After 5 days of once daily dosing there was a statistically significant increase in plasma omeprazole AUC for the 20-mg PO ($P = 0.018$) and 40-mg IV ($P = 0.013$) doses, but no significant change was seen with the 10-mg IV dose (Table 2; Figure 4). The bioavailability for the 20-mg oral dose was significantly increased from 57% on day 1 to 84% on day 5 ($P = 0.044$), and the clearance for the 40-mg IV dose had decreased by 43% from 446 to 237 mL/min ($P = 0.013$). The plasma elimination half-life was also significantly ($P = 0.033$) prolonged by 34% for the 40 mg IV dose (Table 2). The volume of distribution was similar for both IV doses, and no significant change occurred during repeated administration (Table 2). The relationship between plasma omeprazole AUC and percent reduction of the integrated 24-hour intragastric acidity is shown in Figure 5. After the first dose there was no significant correlation ($r = 0.002$; $P = 0.993$). On day 5 the correlation was statistically significant ($r = 0.449$; $P = 0.0186$) but far from close.

Tolerability

Omeprazole was well tolerated by the patients, and no clinically significant changes in laboratory variables were found. Adverse experiences were few, and none was considered serious, clinically important, or related to drug exposure.

Discussion

The present study showed that the effect of both IV and PO omeprazole on 24-hour intragastric acidity increases during repeated once daily administration. Plasma concentrations of omeprazole were markedly and significantly increased by >80% during repeated dosing with 20 mg PO and 40 mg IV, whereas no significant change (+17%) was seen during repeated dosing with 10 mg IV. Despite this fact, there was a pronounced increase in effect on intragastric acidity during repeated dosing even for the 10-mg IV dose.

The finding of an increased antisecretory effect during repeated administration is in agreement with previous studies with both PO[8–11] and IV[11] administration of omeprazole. In some studies increased plasma concentrations were found[8,9,11,12] but not in others.[4] Omeprazole itself does not inhibit the gastric proton pump (H^+,K^+-ATPase) but has to be converted to its active sulfenamide form.[13] This conversion takes place in the very acidic space of the secretory canaliculi in the parietal cell.[13] The sulfenamide

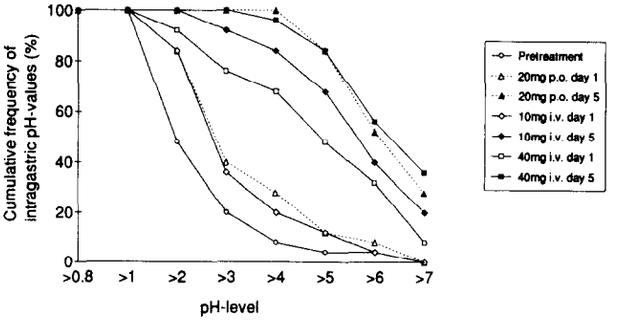

Figure 2. Median cumulative relative frequency of intragastric pH values in nine patients with duodenal ulcer before and during once daily treatment with omeprazole.

Table 1. Integrated 24-Hour Intragastric Acidity, Percent Reduction Compared With Pretreatment, and Percent Time Above pH 4 and 7

		20 mg PO		10 mg IV		40 mg IV	
	Pretreatment	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
AUC (H^+)	258	108	0.15	129	18.1	49.1	0.09
($mmol \cdot h \cdot L^{-1}$)	(102–435)	(1.28–495)	(0.004–22.9)	(0.11–358)	(0.10–122)	(0.01–312)	(0.01–188)
Reduction (%)	—	43.2	99.9	54.8	95.7	88.4	99.9
		(−25.5–98.8)	(94.2–99.9)	(−89.1–99.9)	(69.1–99.9)	(−21.1–99.9)	(56.9–99.9)
Time above	8	28	100	20	84	68	96
pH 4 (%)	(0–36)	(8–84)	(68–100)	(4–100)	(52–100)	(12–100)	(44–100)
Time above	0	0	28	0	20	8	36
pH 7 (%)	(0–4)	(0–16)	(4–44)	(0–4)	(0–40)	(0–32)	(0–48)

NOTE. Values are given as median and range.

form binds covalently to the H^+,K^+-ATPase, inactivating the proton transport.[13] This covalent binding causes a duration of antisecretory effect that is much longer than the presence of omeprazole in plasma.[4] Because of this long duration of action, acid secretion will still be inhibited 24 hours after dose.[4] It has previously been suggested[11] that this will lead to a gradual increase in the degree of acid inhibition during the first days of once daily dosing because of an increase in the number of enzymes inhibited. Because of this initial accumulation of enzyme inhibition, an increase in the degree of acid inhibition is anticipated even with unchanged plasma concentrations of omeprazole. An increase in plasma omeprazole concentration will further accentuate this initial increase in acid inhibitory effect.

Increased plasma omeprazole concentrations have previously been reported both after once daily PO[8–10,12] and IV[11] administration. One important pathway for the hepatic metabolism of omeprazole is via the enzyme IIC18 in the cytochrome P-450 enzyme family,[14,15] and it has previously been suggested that the increased plasma concentrations of omeprazole, seen during the first days of once daily dosing, are caused by an inhibition by omeprazole of this metabolic pathway.[11,16] In the present study

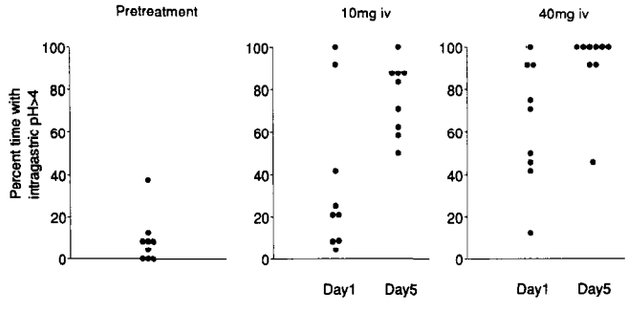

Figure 3. Individual patient data on percent time with an intragastric pH > 4 during each 24-hour experiment.

plasma omeprazole concentration AUC was significantly increased by >80% during IV dosing with 40 mg, whereas no significant increase was seen after repeated IV administration of 10 mg omeprazole, suggesting that the possible effect on P-450 IIC18 is dose dependent.

In the present study there was no close relationship between the degree of reduction of integrated 24-hour intragastric acidity and plasma omeprazole AUC although the correlation reached statistical significance on day 5. This is in contrast to a previous study in which a very close relationship was found between the degree of reduction of pentagastrin-stimulated acid output, measured 2–4 hours after dose, and plasma omeprazole AUC.[4] One possible explanation for this discrepancy is the difference in length of time during which these measurements were performed. The reduction of 24-hour intragastric acidity is dependent both on the initial degree of inhibition of acid secretion as well as the duration of acid inhibition. The close correlation between reduction of peak acid output and plasma omeprazole AUC found 2–4 hours after dose suggests that the initial degree of acid inhibition is dependent on the systemic availability and hence parietal cell availability of omeprazole. However, omeprazole was almost cleared from plasma within 3–5 hours and the duration of acid inhibition is most likely only determined by the rate of regeneration and/or reactivation of the proton pumps. It seems reasonable to assume that the rate of recovery of acid secretion will vary among individuals independent of what plasma omeprazole concentrations were during the first 5 hours after dose, therefore significantly distorting the relationship between plasma omeprazole AUC and antisecretory effect. Another possibility is that the day-to-day variations in 24-hour intragastric acidity are much greater than those for stimulated acid output, leading to imprecisions in the determination of the true reduction. This latter possibility is

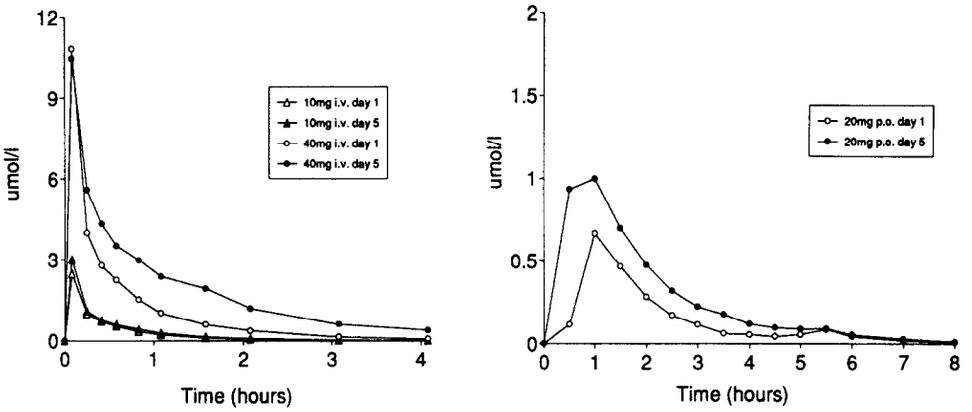

Figure 4. Mean plasma omeprazole concentration-time curve in nine patients with duodenal ulcer during once daily administration of omeprazole.

supported by the fact that three patients had higher acidity levels after the first dose than in the pretreatment experiment, leading to an estimated reduction of up to −89%, i.e., an increase (see Table 1). It has been reported that there is a good reproducibility of repeated tests of intragastric acidity both using the aspiration technique[17] and intragastric pH electrodes[18]; however, these conclusions were based on the reproducibility of the group mean or median value and not on the reproducibility in individual patients or subjects. The data published by Merki et al.[18] show that the day-to-day variation in median intragastric acidity in the same individual can vary by >50%. Such variations would markedly influence the estimation of an individual patients response (i.e., change in relation to pretreatment or placebo) to an antisecretory agent and distort the relationship between plasma concentrations and pharmacological response.

The previous suggestion that IV omeprazole was less potent than PO omeprazole[2] in reducing 24-hour intragastric acidity could not be confirmed in this present comparative study. In contrast to previous results,[2] IV omeprazole appears to be twice as potent, a finding consistent with the 50% bioavailability of the 20-mg PO dose on day 1. The discrepancy between our results and those previously published is most likely caused by the lack of a direct comparison; also, results from single dose IV studies have been compared with those of studies using repeated PO administration. Thus, when determining the optimal regimen of omeprazole dosing for acid inhibition, the route and duration of administration must be taken into consideration, together with the dose of omeprazole; after 5 days of once daily administration doses as low as 10 mg IV and 20 mg PO are effective and dependable in reducing 24-hour intragastric acidity in patients with duodenal ulcer.

One potential indication for IV omeprazole is as an alternative dosage form in patients who cannot take PO medication. The recommended dose should in this instance mimic the antisecretory effects of the recommended PO dose for the specific indication. The results of the present study show that the reduction of 24-hour intragastric acidity during IV administration of 10 mg omeprazole is comparable with that seen during oral treatment with 20 mg, both on day 1 and 5. However, for both these doses it takes

Table 2. Omeprazole Pharmacokinetic Variables in Nine Patients With Duodenal Ulcer

	20 mg PO		10 mg IV		40 mg IV	
	Dose 1	Dose 5	Dose 1	Dose 5	Dose 1	Dose 5
AUC ($\mu mol \cdot h \cdot L^{-1}$)	1.00 (0.65–1.56)	1.88 (1.15–3.05)	0.99 (0.79–1.24)	1.17 (0.88–1.54)	4.32 (3.32–5.63)	8.14 (5.64–11.76)
Clearance (*mL/min*)	—	—	487 (390–608)	414 (313–547)	446 (343–581)	237 (164–342)
Bioavailability (%)	57 (35–80)	84 (64–103)				
$t_{1/2}$ (*h*)	—	—	0.62 (0.45–0.83)	0.66 (0.56–0.78)	0.79 (0.72–0.88)	1.06 (0.82–1.35)
V_{SS} (*L*)	—	—	18.6 (14.2–24.3)	17.2 (13.4–22.2)	20.1 (14.4–28.0)	18.9 (15.1–23.7)

NOTE. Values are given as geometric mean with 95% confidence interval.

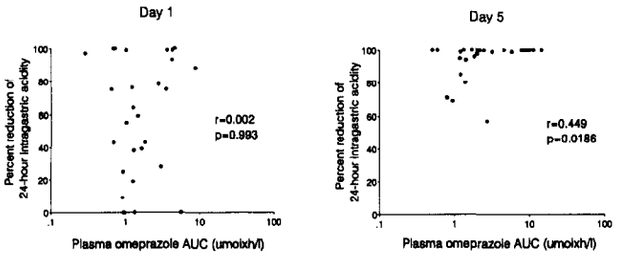

Figure 5. Relationship between individual values of the area under the plasma omeprazole concentration-time curve (AUC) and the percent reduction of pretreatment integrated 24-hour intragastric acidity after the first and fifth once daily dose of omeprazole, 10 mg IV, 20 mg PO, and 40 mg IV, in nine patients with duodenal ulcer disease. Each patient is represented with a total of six dots.

3–5 days before the maximal effect is obtained.[4] Patients in need of parenteral treatment are usually severely ill, and a prompt and effective reduction in acid secretion already during the first day of treatment is often warranted. A starting dose of 40 mg IV will, according to the results in the present study, produce a more marked and prompt reduction than 10 mg IV. If treatment is to be continued for more than 3–5 days, a reduction in dose to 10 mg IV can probably be done without any major decrease in antisecretory effect.

Other potential indications in which IV administration is usually a necessity are prevention of stress-related gastric mucosal injury in intensive care unit patients and treatment of upper gastrointestinal bleeding caused by peptic lesions. A profound reduction of intragastric acidity has for many years been thought beneficial in these indications,[19,20] despite inconsistent results from clinical trials with H_2-receptor antagonists.[21] It has been suggested that acid secretion should be reduced to such an extent that the intragastric pH is kept above 4.[19] However, none of the IV doses used in the present study were capable of continuously maintaining intragastric pH above 4 in all patients during the first day of treatment. A previous study in fasting patients with duodenal ulcer has shown similar results.[3] These data therefore suggest that IV administration of omeprazole must be given in higher doses and/or more frequently than once daily to achieve this goal in all patients during the first day of treatment.

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