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Pharmacokinetics of Oral and Intravenous Omeprazole in Patients With the Zollinger–Ellison Syndrome

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The pharmacokinetics and pharmacodynamics of oral and IV omeprazole after a single dose were studied in 9 patients with the Zollinger–Ellison syndrome to determine whether the increased dose required to control gastric acid hypersecretion could be explained on the basis of altered pharmacokinetics. Each patient was studied both after receiving a single IV bolus of omeprazole (40 mg) and after receiving a single oral dose of omeprazole (80 mg). Intravenous and oral omeprazole doses were administered 1 week apart. Gastric acid secretion and plasma concentrations of omeprazole after drug administration were determined in each patient. The area under the plasma concentration curve, clearance, and volume of distribution after IV omeprazole administration and the area under the plasma concentration curve, peak plasma concentration, and time required to reach the peak after oral omeprazole administration were not different from those reported previously for normal subjects and patients with peptic ulcer disease. Mean (±SEM) bioavailability of oral omeprazole for all patients was 68% ± 16%, which was similar to the bioavailability reported previously for normal subjects. Three patients had a significantly lower bioavailability (20% ± 8%) than the others, and their basal acid outputs were significantly higher than those of the other 7 patients. For all patients there was an inverse correlation between bioavailability and basal acid output ($r = 0.76$; $P < 0.02$). The mean (±SEM) elimination half-lives of IV and oral omeprazole were not different (2.3 ± 0.4 vs. 2.4 ± 0.5 hours) but were significantly longer than those reported previously for normal subjects ($P < 0.02$). The duration of action correlated with the elimination half-life of the drug ($r = 0.87$; $P < 0.003$) and area under the plasma concentration curve ($r = 0.72$; $P < 0.03$). The mean durations of action of IV and oral omeprazole were not significantly different (34 ± 7.2 vs. 35 ± 6.2 hours). It was concluded that altered pharmacokinetics do not account for the increased drug requirement of omeprazole in patients with the Zollinger–Ellison syndrome. In contrast to a previous study, the oral and IV omeprazole had the same duration of action, suggesting that intermittent bolus administration of parenteral omeprazole will obviate the need for continuous infusion of histamine H_2-receptor antagonists in patients requiring parenteral antisecretory drugs. Furthermore, an IV dose every 12 hours controlled acid secretion in all patients, suggesting this as the recommended dose interval in patients requiring parenteral drug therapy.

Omeprazole, a substituted benzimidazole, has become the drug of choice to control acid hypersecretion in patients with the Zollinger–Ellison syndrome (ZES) and other gastric hypersecretory states (1–7). The mechanism of inhibition of acid secretion involves the formation of the stable enzyme inhibitor complex between acid-generated sulfenamide of omeprazole and hydrogen-potassium-stimulated adenosine triphosphatase (H^+,K^+-ATPase) on the parietal cell (1,8–13). Omeprazole is absorbed from small intestine with approximately 50% bioavailability after oral administration of the encapsulated form of the drug (1). Although the half-life of omeprazole in plasma is about 60 minutes, the duration of action of

Abbreviations used in this paper: Vd_{ss}, steady-state volume of distribution; ZES, Zollinger–Ellison syndrome.

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omeprazole following a single dose exceeds 24 hours because of the stable enzyme inhibitor complex (14). Therefore, unlike histamine H_2-receptor antagonists, in which there is a good correlation between plasma concentration of the drug and its antisecretory effect (15,16), acid inhibition does not correlate with plasma concentration of the drug and its antisecretory effect (17). However, the area under the plasma omeprazole concentration curve has been shown to correlate with the magnitude of the acid inhibition (18). In patients with ZES, even though oral omeprazole will control the acid hypersecretion in all cases with once- or twice-daily dosing (2–7), two problems still remain.

First, compared with most patients with idiopathic peptic ulcer disease, most patients with ZES require higher doses of oral omeprazole indefinitely. In addition, in a proportion of patients, there is an increase in drug requirement with time (3–7). A similar high dose of histamine H_2-receptor antagonists is also required in patients with ZES (19–24) and can possibly be explained on the basis of altered pharmacokinetics for these drugs in up to 80% of patients with ZES (15,25,26). It is unknown whether a similar alteration in the pharmacokinetics of omeprazole is responsible for the increased drug requirement.

Second, most patients with ZES require a parenteral antisecretory drug at some time because of either chemotherapy or surgery (3,27,28). Parenteral histamine H_2-receptor antagonists are frequently effective in high doses and, unfortunately, in most cases must be administered by continuous IV infusion (29,30). Intravenous omeprazole has recently become available. One study in normal subjects (31) suggests that it may be as potent and have the same duration of action as the oral form, whereas other studies (32,33) suggest that it may be less potent and have a shorter duration of action, possibly limiting its potential usefulness in patients with ZES requiring parenteral antisecretory therapy.

To address these two problems, we carried out a randomized, prospective study comparing the pharmacokinetics and pharmacodynamics of oral and IV omeprazole in patients with ZES to gain insight into whether altered pharmacokinetics of omeprazole contribute to the increased dose requirement and to determine whether oral and IV omeprazole are equally effective.

Patients and Methods

Patients

Nine patients with ZES were studied after giving written informed consent for a protocol approved by the Institutional Human Research Review Committee of the National Institutes of Diabetes, Digestive and Kidney Diseases. The criteria for the diagnosis of the ZES used in these patients were a basal acid output of >15 mEq/h in patients who had not undergone gastric surgery or a basal acid output of >5 mEq/h in patients with previous gastric surgery, a fasting serum gastrin concentration of >100 ng/L (>100 pg/mL) [normal, <100 ng/L (<100 pg/mL)] with a positive secretin test, positive calcium infusion test, histological evidence of gastrinoma, or a combination of these (19). Before entering the study, each patient underwent a physical examination, electrocardiogram, laboratory evaluation including complete blood count, urinalysis, serum chemistry profile, fasting serum gastrin concentration, and upper gastrointestinal endoscopy. Imaging studies (ultrasound, computed tomographic scan with contrast, selective abdominal angiography) were performed to assess tumor location and extent as described previously (34,35).

Study Design

Each patient was randomly assigned to receive a single IV dose (40 mg) or a single oral dose (80 mg) of omeprazole on separate occasions with a 1-week period between administrations. Two patients received an additional 80-mg IV dose 1 week later to assess the effect of omeprazole dose on the pharmacokinetics. All antisecretory medications were discontinued for at least 12 hours before the study. The IV formulation (40 mg) of omeprazole was a freeze-dried preparation that was solubilized by the addition of polyethylene glycol before administration. The oral formulation (80 mg) consisted of commercially available enteric-coated granules in hard gelatin capsules. After an overnight fast, a nasogastric tube was placed in the dependent part of the stomach. Each patient received IV fluids consisting of 5% (wt/vol) dextrose, 0.9% (wt/vol) saline, and 20 mEq/h of potassium chloride at 125 mL/h plus the volume of gastric output for the previous hour. Basal acid output was determined for 1 hour, as described previously (36), followed by either an IV bolus or an oral dose of omeprazole.

After IV omeprazole administration, gastric acid output was measured hourly for 8 hours and then every 2 hours for up to 24 hours if the gastric acid output was <10 mEq/h (or <5 mEq/h in patients with previous gastric surgery). If the gastric acid output became >10 mEq/h before 24 hours, measurements were continued at 8-hour intervals for 1 hour for an additional 48 hours or until basal acid output was >30 mEq/h or $>50\%$ of the baseline basal acid output. The same measurements were taken in patients whose gastric acid output remained <10 mEq/h at the end of the initial 24 hours. After oral omeprazole administration, the nasogastric tube was clamped for 3 hours to allow for gastric emptying and drug absorption followed by hourly acid output measurements for 5 hours. Thereafter, acid output was measured every 2 hours for up to 24 hours, and the same criteria were used for obtaining further acid output measurements as described for the IV arm of study.

To assess the pharmacokinetics of omeprazole, serial blood samples were obtained at the following time points: IV, 0, 2, 4, 5, 10, 20, 30, and 60 minutes, then every hour for 8 hours followed by every 2 hours for up to 24 hours; oral, 0, every 30 minutes for the first 3 hours, then every hour for up to 8 hours, and finally every 2 hours for up to 24 hours. Each

timed sample consisted of 4 mL of blood which was placed into heparinized tubes and centrifuged with the plasma fraction stored at 20°C until analysis. Plasma concentrations of omeprazole were determined by high-performance liquid chromatography as previously described (37). The sensitivity of the method is 5 ng/mL or 0.014 μmol/L with overall intraday and interday variability of < 7%.

Omeprazole Pharmacokinetics

The pharmacokinetics of omeprazole was analyzed by noncompartmental analysis (38). The elimination half-life ($t_{1/2}$) was determined from semilogarithmic plots of plasma concentration vs. time: $t_{1/2} = 0.693/K$ elimination, where K elimination (K_{el}) is the slope of a linear least-squares regression line through the terminal portion of the plots. The area under the concentration-time curve (AUC) was estimated by the trapezoidal rule from time zero to the last measurable sample and extrapolated to infinity by the relationship of C_{last}/K_{el}, where C_{last} is the last measurable concentration. The total plasma clearance was calculated after IV administration by dividing the dose by the AUC estimate. The steady-state volume of distribution (Vd_{ss}) was determined by the following equation: Vd_{ss} = (AUMC)(dose)/AUC^2, where AUMC is the area under the moment curve (38). After oral administration the pharmacokinetic parameters determined included the observed peak concentration (C_{max}), the time to reach the peak after dosing (t_{max}), and the bioavailability (F), which was calculated from the ratio of dose-normalized AUC values for oral and IV administration.

Comparisons between differences were made using the Student's t test. Differences of $P < 0.05$ were considered significant.

Results

Patients

The clinical and laboratory characteristics of these patients are listed in Table 1. The patients in the present study closely resemble the entire group of patients with ZES followed by the National Institutes of Health in terms of age, sex, tumor status, serum gastrin concentration, and basal and maximal gastric acid output (16). The mean age was 52 years (range, 33–71 years) and the mean body weight was 84 kg (range, 53–127 kg). Mean basal acid output was 42 mEq/h (range, 27–69 mEq/h) and maximal acid output was 69 mEq/h (range, 38–100 mEq/h). Median serum gastrin concentration was 749 ng/L (749 pg/mL) [range, 468–23,600 ng/L (468–23,600 pg/mL)]. Two patients had multiple endocrine neoplasia type 1 (patients 1 and 8) and three patients had tumor proven by laparotomy and biopsy. All patients were treated with histamine H_2-receptor antagonists (mean dose ranitidine, 3800 mg/day) for at least 2 weeks before entering the study. Two patients (patients 1 and 4) had undergone previous gastric surgery: patient 1 a parietal cell vagotomy and patient 4 a Billroth I gastrectomy and vagotomy.

Pharmacodynamic Studies

Intravenous omeprazole. In all 9 patients, the action of IV omeprazole (40 mg) was rapid in onset, resulting in a marked inhibition of basal gastric acid secretion of 81% ± 4% and 96% ± 2% (mean ± SEM), respectively, 1 and 2 hours after administration of the drug (Figure 1). In 7 patients (patients 1–7; Table 1), omeprazole produced prolonged and effective gastric acid inhibition (< 10 mEq/h in patients without previous gastric surgery and < 5 mEq/h in patients with previous gastric surgery) lasting 16–24 hours (Table 2). However, in 2 patients (patients 8 and 9; Table 1), gastric acid secretion was inhibited effectively (< 10 mEq/h) for < 8 hours after IV administration of the drug (Table 2).

Oral omeprazole. A single oral dose of omeprazole (80 mg) caused inhibition of basal gastric acid secretion of 76% ± 8% and 87% ± 6% (mean ± SEM), respectively, at 4 and 5 hours after administration of the drug (Figure 2). In 7 patients (patients 1–7; Table 1), a single dose of omeprazole produced prolonged

Table 1. Clinical and Laboratory Characteristics of Patients With the Zollinger–Ellison Syndrome

Patient no.	Age (*yr*)/sex	Weight (*kg*)	Fasting serum gastrin (*pg/mL*)	BAO/MAO (*mEq/h*)	MEN-I[a]/tumor[b] present	Ranitidine dose
1	60/M	83	2175	64/88	+/−	900 mg every 6 h
2[b]	71/F	53	23600	29/38	−/+	600 mg every 6 h
3	61/M	55	1443	37/84	−/−	750 mg every 6 h
4[b]	41/M	97	780	53/51	−/+	750 mg every 6 h
5	52/F	80	604	27/51	−/−	1500 mg every 6 h
6	61/M	87	567	28/81	−/−	900 mg every 6 h
7[b]	40/F	127	468	38/40	−/−	1500 mg every 6 h
8	33/M	94	749	69/93	+/+	1500 mg every 6 h
9	52/F	85	576	29/100	−/−	150 mg every 6 h

BAO, basal acid output; MAO, maximal acid output; MEN-I, multiple endocrine neoplasia type 1.

[a]Presence or absence established by family history and serial serum calcium and parathyroid hormone measurements as outlined in Patients and Methods.

[b]Tumor proven on the basis of laparotomy and histology.

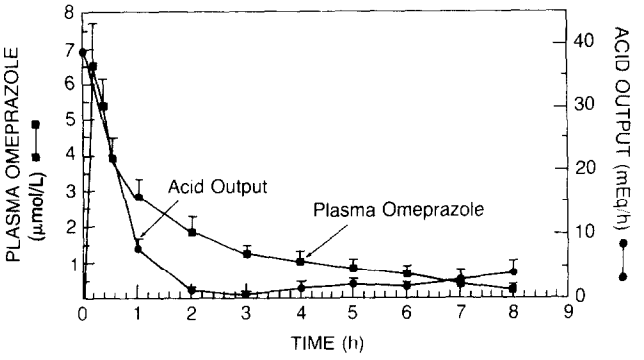

Figure 1. Acid output and plasma omeprazole concentration after a single IV dose of omeprazole (40 mg) in patients with ZES. Acid output was measured hourly for 2 hours before and 8 hours after omeprazole administration. Plasma omeprazole concentration was determined, as outlined in Patients and Methods, at the indicated times. Values are means from 9 patients. *Vertical bars* represent 1 SEM.

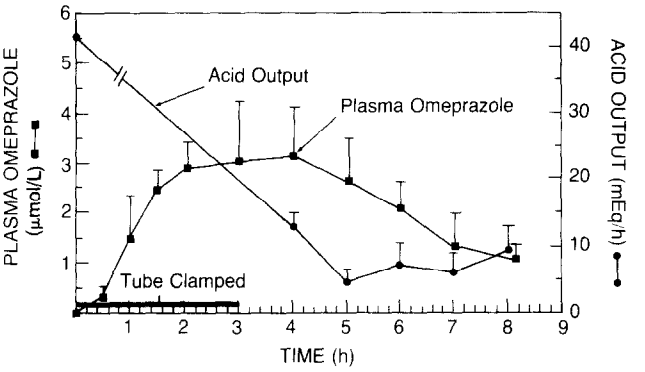

Figure 2. Acid output and plasma omeprazole concentration after a single oral dose of omeprazole (80 mg) in patients with ZES. Acid output was measured hourly for 2 hours before oral omeprazole administration. The nasogastric tube was clamped for 3 hours to allow for gastric emptying, then gastric acid secretion was measured hourly for 5 hours. Plasma omeprazole concentration was determined, as described in Patients and Methods, at the indicated times. Values are means from 9 patients. *Vertical bars* represent 1 SEM.

and effective gastric acid inhibition (<10 mEq/h in patients without previous gastric surgery and <5 mEq/h in patients with previous gastric surgery) lasting for 20–24 hours (Table 3). However, in 2 other patients (patients 8 and 9; Table 1), gastric acid secretion was inhibited effectively (<10 mEq/h) for <8 hours after oral omeprazole administration (Table 3).

To determine whether the duration of action of IV omeprazole differs from that of oral omeprazole, the degree of acid inhibition caused by a single dose of IV omeprazole (40 mg) and oral omeprazole (80 mg) was analyzed by two criteria (Table 4): (a) time from the onset of action of the drug to the point of the first increase in gastric acid output (>1 mEq/h) and (b) time from the onset of action of the drug to the time when the gastric acid output was one half of the basal acid output before drug administration. Using the first or second criterion for duration of action of the drug, the mean durations of action of IV omeprazole and oral omeprazole were not significantly different (17 ± 3.7 vs. 20.5 ± 3.8 hours, $P > 0.1$, and 34 ± 7.2 vs. 34 ± 6.2 hours, $P > 0.1$, respectively).

Pharmacokinetic Studies

To examine whether an increased dose requirement for omeprazole in patients with ZES might be caused by altered pharmacokinetics of the drug, we analyzed the pharmacokinetics of IV and oral omeprazole administration in the 9 patients with ZES.

Intravenous omeprazole. Figure 1 shows the mean plasma concentration–vs.–time curve of omeprazole up to 8 hours after administration of a 40-mg IV

Table 2. Relationship Between Gastric Acid Output and Plasma Omeprazole Concentration at Various Times After a Single Intravenous Dose (40 mg) of Omeprazole in Patients With the Zollinger–Ellison Syndrome

	Time after drug administration									
	8 h		12 h		16 h		20 h		24 h	
Patient no.	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)
1	0	0.12	2	0.20	2.4	0.12	11.8	0.09	21.1	0.05
2	1	0.52	0	0.14	0	0.06	0	ND	2.4	ND
3	0	0.60	0	0.15	2	0.03	1.6	ND	2.0	ND
4	0	—	0	0.33	0	0.16	0	0.12	0	0.09
5	0	0.13	0.4	ND	1.26	ND	7.1	ND	15.3	ND
6	0	ND	6.4	ND	5.7	ND	4.4	ND	16.6	ND
7	0	1.4	0	0.6	0	0.4	0	0.2	0.4	ND
8	8.5	ND	15.8	ND	31	ND	—	ND	—	ND
9	20	0.014	—	ND	—	ND	—	ND	—	ND
Mean ± SEM	3.3 ± 2.5	0.46 ± 0.23	3.1 ± 2.1	0.28 ± 0.01	5.3 ± 4.0	0.15 ± 0.07	3.6 ± 1.8	0.14 ± 0.03	8.3 ± 3.7	<0.05

ND, not detectable; —, sample value not determined.

Table 3. Relationship Between Gastric Acid Output and Plasma Omeprazole Concentration at Various Times After a Single Oral Dose (80 mg) of Omeprazole in Patients With the Zollinger–Ellison Syndrome

	Time after drug administration									
	8 h		12 h		16 h		20 h		24 h	
Patient no.	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)	Acid output (*mEq/h*)	Omeprazole concentration (*μmol/L*)
1	0	0.47	0	0.08	1	ND	3.3	ND	11.6	ND
2	0	3.1	0	0.98	0	0.34	0	0.13	0.5	0.05
3	0	2.1	0	0.54	1.7	0.13	0.3	0.04	1	ND
4	14.4	0.3	17.4	0.3	4.8	0.16	1.5	0.12	5.5	0.07
5	20.9	0.8	0	0.27	0	0.08	0	ND	0.3	ND
6	0	0.56	0	0.06	0	ND	0	ND	1.9	ND
7	0	3.25	0	1.03	0	0.49	0	0.23	0.3	0.16
8	36.6	0.07	—	0.23	—	0.05	—	ND	0	ND
9	18.5	0.08	—	ND	—	ND	—	ND	—	ND
Mean ± SEM	10 ± 4.8	1.19 ± 0.45	2.5 ± 2.7	0.43 ± 0.15	1.1 ± 0.7	0.2 ± 0.08	0.7 ± 0.5	0.13 ± 0.05	2.6 ± 1.5	<0.05

ND, not detectable; —, sample value not determined.

bolus dose of omeprazole in the 9 patients. After a single dose, plasma concentration of omeprazole declined in a biexponential manner with a rapidly declining distributional phase followed by an elimination phase (Figure 1). Two patients also received an 80-mg IV dose of omeprazole; when the AUC was normalized for the dose and compared with the AUC of the 40-mg dose, the results suggested linear pharmacokinetics, but further studies will be necessary to verify this observation. Table 5 shows the estimates of various pharmacokinetic parameters after a single IV dose (40 mg) of omeprazole. The (mean ± SEM) AUC was 16.8 ± 4.0 μmol/L (h) [range, 2.42–31.8 μmol/L (h)], clearance was 16.5 ± 7.5 L/h (range, 3.6–67.9 L/h), Vd_{ss} was 0.30 ± 0.06 L/kg (range, 0.06–0.61 L/kg), and $t_{1/2}$ was 2.3 ± 0.4 hours (range, 0.8–4.3 hours).

Table 4. Duration of Action of Intravenous and Oral Omeprazole

	Time to first increase in acid output (*h*)		Time to half-basal gastric acid output (*h*)	
Patient no.	IV	Oral	IV	Oral
1	12	16	32	32
2	24	32	40	56
3	16	16	48	48
4	32	22	72	40
5	16	32	24	40
6	10	24	19	32
7	32	32	48	48
8	7	6	16	8
9	4	4.5	7	6
Mean ± SEM	17 ± 3.7	20.5 ± 3.8	34 ± 7.2	34 ± 6.2

NOTE. Duration of action was analyzed as the time from the onset of action of the drug to the time of the first > 1-mEq/h increase in gastric acid output or as the time from the onset of action of the drug until the gastric acid output reached one half of the pretreatment basal acid output.

Oral omeprazole. Figure 2 shows the mean plasma concentration–vs.–time curve of omeprazole up to 8 hours after oral administration of 80 mg of the drug in 9 patients with ZES. After a single dose of omeprazole, C_{max} was 3.9 ± 1.0 μmol/L (range, 0.39–8.4 μmol/L) and t_{max} was 3.50 ± 0.44 hours (range, 1.5–5 hours). Table 5 shows the estimates of various pharmacokinetic parameters after a single oral dose (80 mg) of omeprazole. The (mean ± 1 SEM) AUC was 21.4 ± 7.1 μmol/L · h^{-1} [range, 2.8–50.4 μmol/L (h)], bioavailability was 0.68 ± 0.16 (range, 0.10–1.37), and $t_{1/2}$ was 2.4 ± 0.5 hours (range, 1.2–5.6 hours). In 3 patients (patients 1, 4, and 8), the bioavailability of the drug was 0.1, 0.14, and 0.35, with a mean bioavailability of 0.19 ± 0.065, which was significantly lower than mean bioavailability of 0.95 ± 0.15 for the other 6 patients ($P < 0.01$). Basal acid output (62 ± 4 mEq/h) was significantly higher ($P < 0.001$) in these 3 patients than in the 6 other patients (31 ± 2 mEq/h). For all patients, there was significant inverse correlation ($r = -0.76$, $P < 0.02$) between the basal acid output of patients before administration of the drug and bioavailability of the drug (Figure 3; Table 5). The regression equation could be described by $y = 1.58 - 0.021x$, where y is the bioavailability and x is the basal acid output before omeprazole administration. In only 1 patient (patient 4; Table 5) was the $t_{1/2}$ of the drug ($t_{1/2}$ = 5.6 hours) more than 2 SD above the mean. This patient had undergone a partial gastrectomy and vagotomy (Billroth I), which may have impaired gastric emptying and absorption. The low bioavailability and increased $t_{1/2}$ might have resulted from slow absorption of the drug.

Table 5. Estimates of Pharmacokinetic Parameters for Intravenous and Oral Omeprazole After a Single Dose in Nine Patients With the Zollinger–Ellison Syndrome

	IV omeprazole				Oral omeprazole		
Patient no.	AUC [μmol/L(h)]	Clearance (L/h)	VD_{ss} (L/kg)	$t_{1/2}$ (h)	AUC [μmol/L(h)]	Bioavailability	$t_{1/2}$ (h)
1	31.3	4.0	0.06	1.8	6.4	0.10	1.7
2	20.2	5.7	0.22	2.5	50.4	1.2	2.8
3	21.7	5.3	0.28	2.1	48.5	1.1	2.1
4	22.6	5.1	0.28	4.2	6.1	0.14	5.6
5	8.0	14.4	0.48	2.0	10.5	0.65	2.6
6	9.1	12.7	0.14	0.8	25.0	1.3	1.6
7	31.8	3.6	0.19	4.3	40.0	0.62	2.6
8	3.9	29.4	0.40	1.2	2.8	0.35	1.5
9	2.4	67.9	0.61	2.2	3.3	0.68	1.2
Mean ± SEM	16 ± 4.0	16.5 ± 7.5	0.30 ± 0.06	2.3 ± 0.4	21.4 ± 7.1	0.68 ± 0.16	2.4 ± 0.5

Relationship Between Pharmacokinetics and Pharmacodynamics of Omeprazole

To investigate whether there were altered pharmacokinetics in patients with ZES and to determine if there was any relationship between plasma concentration of omeprazole and its gastric antisecretory effect, blood samples were drawn at various times to measure plasma omeprazole concentrations. Figure 1 and Table 2 show the results of the plasma concentration of omeprazole measured at various times up to 24 h and gastric acid output measured at corresponding times after a single IV dose (40 mg) of omeprazole, and Figure 2 and Table 3 show the results after a single oral dose of omeprazole (80 mg). As shown in Tables 2 and 3, comparison of plasma omeprazole concentrations with the degree of acid inhibition for all patients in the time 8–24 hours after drug administration showed no significant correlation when analyzed by least-squares analysis ($r = 0.6$; $P > 0.2$). Significant correlations also were not found for individual patients both for oral and IV omeprazole (Tables 2 and 3).

To investigate whether the pharmacokinetic parameters of the drug such as AUC or terminal $t_{1/2}$ correlated with pharmacodynamic effects of the drug such as efficacy and duration of action, we compared the terminal $t_{1/2}$ and AUC obtained after a single IV dose (40 mg) of omeprazole with the duration of action of the drug and degree of acid inhibition at 24 hours (Figure 4). When the duration of action was expressed as time in hours after drug administration from the onset of action of the drug to the time of first > 1-mEq/h increase in gastric acid output (Figure 4*A*)

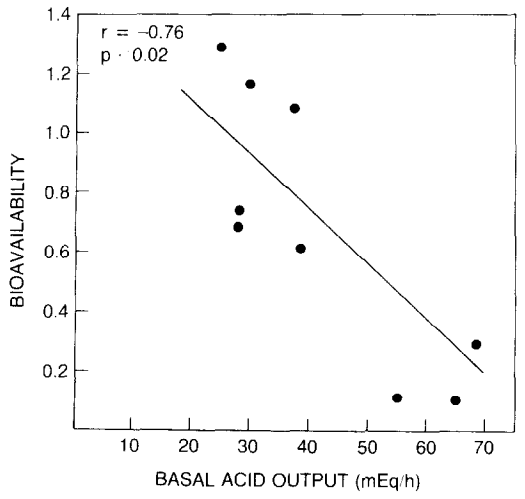

Figure 3. Relationship between basal acid output and the bioavailability of omeprazole. Bioavailability was calculated, as outlined in Patients and Methods, in 9 patients with ZES (patients 1–9; Table 1).

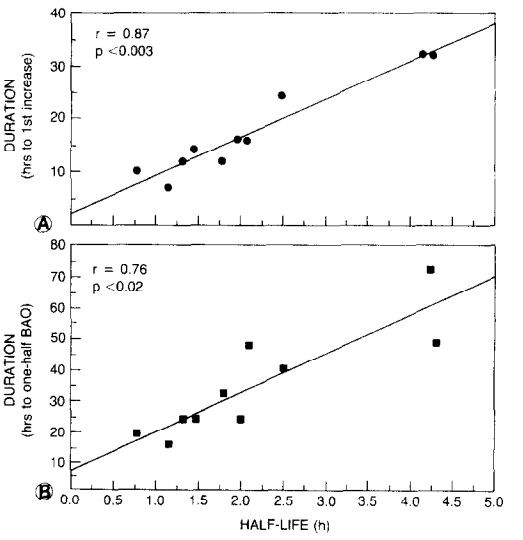

Figure 4. Relationship between plasma $t_{1/2}$ of IV omeprazole and its duration of action in patients with ZES. The duration of action of the drug was defined as the time (hours) to the first > 1-mEq/h increase in acid output after drug administration from the onset of action of the drug (*A*) or as the time required (hours) after drug administration for the acid output to reach at least one half of the basal acid output before omeprazole administration (*B*). Linear regression and correlation coefficients (*r*) were determined by least-squares analysis.

or as the time in hours required after drug administration to reach one half of the basal acid output before drug administration (Figure 4*B*), there was a highly significant correlation with the omeprazole $t_{1/2}$ ($r = 0.87$, $P < 0.003$, $y = 7.4x + 0.41$, and $r = 0.76$, $P < 0.02$, $y = 12.8x + 4.1$, respectively). As shown in Figure 5, when the AUC after IV omeprazole administration was compared with the duration of action of the drug expressed as time in hours to the first >1-mEq/h increase in acid output after administration (Figure 5*A*) or as the time in hours required after drug administration to reach one half of the basal acid output before drug administration (Figure 5*B*), there also was a highly significant correlation ($r = 0.69$, $P < 0.05$, $y = 0.63x + 6.4$, and $r = 0.72$, $P < 0.01$, $y = 1.3x + 12.1$, respectively). However, there was no correlation between AUC and percent inhibition of gastric acid at 24 hours ($r = 0.25$; $P > 0.05$; n = 7).

Discussion

The present study of patients with ZES had two main purposes: (a) to compare the ability of parenteral omeprazole with that of oral omeprazole in inhibiting gastric hypersecretion, and (b) to investigate the pharmacokinetics of omeprazole to determine whether altered pharmacokinetics of omeprazole could explain the increased omeprazole dose required to control acid hypersecretion in patients with ZES.

In regard to the first aim, patients with ZES may be unable to take oral medication at times and would require parenteral histamine H_2-receptor antagonists. High doses of parenteral histamine H_2-receptor antagonists are frequently required by continuous infusion

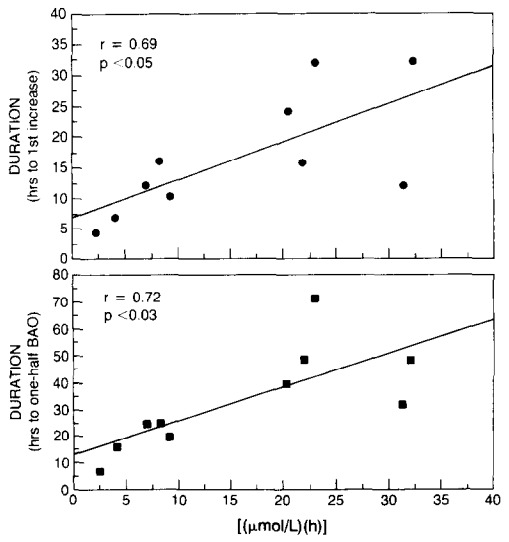

Figure 5. Relationship between AUC and duration of action of IV omeprazole in patients with ZES. Duration of action was defined as the time required (hours) after drug administration to reach one half the basal acid output before drug administration.

(29,30), which in some cases may be required for weeks (30). Furthermore, gastric acid secretion can rebound rapidly if the infusion of histamine H_2-receptor antagonist is stopped inadvertantly. With IV omeprazole, intermittent bolus administration of omeprazole once or twice a day would be safer and simplify management of the control of gastric acid hypersecretion in these patients.

A recent study in normal subjects (31) reported that the bioavailability of IV omeprazole was twice that of oral omeprazole. However, reports on the potency and duration of action of IV omeprazole are conflicting (31–33). A study in normal subjects reported that 10 mg of IV omeprazole was as potent as 20 mg of oral omperazole and both forms had the same duration of action (31). However, studies in patients with idiopathic duodenal ulcers reported that IV omeprazole was less potent and had a shorter duration of action than oral omeprazole (32,33,41). In these latter studies, inhibition of acid secretion by 95% required only 30 mg of oral omeprazole once a day, but 80 mg of IV omeprazole every 12 hours was needed to achieve the same degree of acid inhibition (32,33,39). In the present study we compared the potency and duration of action of IV and oral omeprazole using a single 40-mg dose administered by IV bolus or an 80-mg dose taken orally. These dosages of omeprazole were chosen based on the report in normal volunteers that the bioavailability of IV omeprazole is twice that of oral omeprazole (31). In our study we found, using both IV and oral omeprazole, that mean basal gastric acid secretion was inhibited by >90% at 12 hours and 70% at 24 hours after administration of the drug. However, the duration of action of IV omeprazole was <24 hours in 6 of 9 patients using time from onset of action of the drug to first increase in acid output after drug administration and in 3 of 9 patients using time from onset of action of the drug to reach postdrug acid output equal to one half the basal acid output before administration of the drug. Because 5 of the 9 patients had gastric acid output exceeding the value for safe control (i.e., >10 mEq/h) at 24 hours after IV omeprazole administration (Table 2) and because of our recent experience in the use of IV omeprazole in controlling gastric acid secretion in patients with ZES during surgery (40), we recommend that IV omeprazole should be administered every 12 hours to inhibit gastric acid secretion adequately.

Patients with ZES require large doses of histamine H_2-receptor antagonists or omeprazole compared with patients with peptic ulcer disease (3,20–24,41–43) and reflux esophagitis (44–46). In the case of histamine H_2-receptor antagonists, it has been proposed (23) and studies have provided some evidence (15,27,47) that the increased dose requirement in patients with ZES could be caused by decreased

bioavailability of the drug, increased drug metabolism, decreased sensitivity of the acid secretory process to the drug (parietal cell resistance), normal initial response with subsequent tachyphylaxis, and increased basal acid output (15,23,26,47). Similar mechanisms may be operative for the increased dose requirement for omeprazole in patients with ZES. To gain insight into whether some of these mechanisms might also contribute to the high dose requirement for omeprazole, we studied the pharmacokinetics of IV and oral omeprazole in patients with ZES.

One explanation for the increased drug requirement could be decreased bioavailability of the drug in some patients due to altered absorption characteristics of the drug. A number of results suggest that altered absorption of omeprazole was not occurring in most patients with ZES. The mean bioavailability of omeprazole in the present study for all patients was 68%, which was not significantly different from the bioavailability of 79% and 54% reported for elderly healthy subjects and young healthy subjects (17). In the present study, 3 patients had low bioavailability and also had decreased AUC. Because 2 of these 3 patients had normal clearance for the drug, low bioavailability in these two patients was probably caused by decreased extent of absorption of the drug. The basal acid outputs in the 3 patients with low bioavailability were significantly higher than basal acid outputs in the 6 other patients. Furthermore, there was a significant inverse correlation between the basal output of all patients and bioavailability of the drug (Figure 3). Despite low bioavailability of the drug, the dosage of omeprazole required in 2 of these 3 patients to adequately control gastric acid secretion was not significantly different from those of the other patients (data not shown). For all patients after a single dose (80 mg) of omeprazole, mean C_{max} was 3.9 ± 1.0 μmol/L, which was twice the value of mean C_{max} of 1.9 ± 0.32 μmol/L obtained in normal healthy volunteers after a 40-mg dose of omeprazole (48). In the present study, mean t_{max} was 3.5 ± 0.4 hours, which was not significantly different from the mean t_{max} of 3.0 ± 0.4 hours reported in the previous study ($P > 0.2$) (48). Therefore, altered absorption characteristics of the drug caused by a decrease in the rate or extent of absorption as a result of either altered gastric motility or high basal acid secretion is not likely to be the basis for the increased requirement for omeprazole in most patients with ZES.

Increased clearance of omeprazole could be another explanation for the increased drug requirement. A number of findings suggest that this was not an important factor in most patients. In the present study, after a single IV dose of omeprazole (40 mg) mean AUC was not significantly different from a mean AUC reported previously using the same IV dose of omeprazole in patients with peptic ulcer disease (32). In the present study, after a single oral dose (80 mg) of omeprazole the mean AUC was 21.4 ± 7.1 μmol/L (h). Previous studies of the pharmacokinetics of oral omeprazole in humans (48–50) have not used 80 mg of omeprazole. However, using a single oral dose of 40 mg of omeprazole, the mean AUC was 10.5 ± 2.4 μmol/L(h), which is approximately one half of the AUC we found in our patients using an 80-mg dose. In the present study, the mean clearance of the drug was not significantly different from that reported for the elderly healthy subjects and young healthy subjects ($P > 0.05$) (17). Therefore, in a majority of patients with ZES, increased drug requirement for omeprazole cannot be contributed to by the rapid clearance of the drug.

Another possible explanation for the increased drug requirement of omeprazole in ZES is a decreased $t_{1/2}$ of omeprazole. Because $t_{1/2}$ is directly related to Vd_{ss} and inversely related to clearance, and because mean clearance in our study is not significantly different from that reported previously (17), we compared the Vd_{ss} of omeprazole in our patients with that reported previously (17,48). In the present study, the mean Vd_{ss} was not significantly different from that reported for the elderly healthy subjects (48) and young healthy subjects ($P > 0.05$) (17). However, the mean $t_{1/2}$ of IV omeprazole was significantly longer than the mean $t_{1/2}$ in normal healthy subjects ($P < 0.01$) (31) but was not significantly different from the $t_{1/2}$ in patients with peptic ulcer disease ($P > 0.05$) (32). The mean $t_{1/2}$ of oral omeprazole was significantly longer than the $t_{1/2}$ reported in young healthy subjects ($P < 0.01$) (17) but was not significantly different from those reported in elderly healthy subjects ($P > 0.05$) (48). The longer $t_{1/2}$ in our patient population than in young healthy subjects reflects the age of our patients, 6 patients being >50 years old. Thus, decreased $t_{1/2}$ due to increased drug elimination is not the basis for increased drug requirement in patients with ZES.

As shown previously in patients with ZES and in animal studies (17), in the present study the degree of acid inhibition was independent of the plasma concentration of omeprazole at various times. Furthermore, in contrast to a previous study in patients without ZES (17), no significant correlation was found between the degree of acid inhibition at 24 hours after administration of omeprazole and AUC. However, a significant correlation was found between the duration of action of omeprazole and AUC and the duration of action and $t_{1/2}$.

It is possible that prolonged treatment with omeprazole may produce tolerance or tachyphylaxis over time, which would explain why some patients require increasing doses of drug after months or years of treatment (6,7). To examine this hypothesis, it would

be necessary to discontinue the administration of omeprazole for weeks or months, which was not feasible in our study.

In conclusion, the present results suggest that altered pharmacokinetics of omeprazole do not explain the increased dose of omeprazole required to control gastric acid secretion in most patients with ZES compared with that required in patients with idiopathic peptic disease. This conclusion is similar to that of a recent study (30) of the use of histamine H_2-receptor antagonists in patients with ZES who require high doses of drug for adequate mucosal healing. In early studies (15,26,48), up to 60% of patients with ZES had altered absorption of histamine H_2-receptor antagonists (with no alterations in clearance, elimination, or metabolism of the drug), suggesting that this might be contributing to the high dose requirements for histamine H_2-receptor antagonists (15). However, subsequent studies showed a very close correlation ($r = 0.96$; $P < 0.001$) between IV and oral doses of histamine H_2-receptor antagonists in this patient population (30), making altered absorption an unlikely cause. Because there is a close correlation ($r = 0.89$; $P < 0.001$) between the doses of oral histamine H_2-receptor antagonist and the dose of oral omeprazole required to control gastric acid hypersecretion in ZES (6), these results suggest that similar mechanisms may be responsible for the high doses of both of these classes of antisecretory drugs. Further studies to understand the basis for this increased drug requirement may become increasingly important because a recent study (51) shows that patients with refractory idiopathic peptic ulcer disease will demonstrate complete healing if high doses of histamine H_2-receptor antagonists are used. This observation suggests that these patients are similar to patients with ZES in having an unexplained high antisecretory drug requirement.

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