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Intravenous Omeprazole in Children: Pharmacokinetics and Effect on 24-Hour Intragastric pH

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ABSTRACT

Background: Omeprazole is a proton pump inhibitor, acting selectively on the gastric parietal cell H^+K^+-adenosine triphosphatase. Data on the intravenous route are limited in children and not available in infants.

Objective: This study was designed to determine the pharmacokinetics and the optimal dosage of intravenous omeprazole in patients younger than 30 months of age.

Methods: Nine children (three girls), aged 4.5 to 27 months, with normal liver and renal functions requiring intravenous omeprazole were studied. After enrollment in the study and randomization, omeprazole was administered once daily, at 8 AM, as a 1-hour infusion. Group 1, consisting of the first four patients, received 20 mg/1.73 m^2, and group 2, consisting of the following five patients, received 40 mg/1.73 m^2. At day 3, a 24-hour intragastric pH and a pharmacokinetic study of omeprazole were performed. Plasma concentrations were measured by high-performance liquid chromatography.

Results: Patients in group 2 had a significantly higher median pH (6.99 vs. 3.35; $P = 0.01$) and percent of monitored time with gastric pH >4 than children given 20 mg/1.73 m^2 (90.6% vs. 44.8%; $P < 0.01$). Four had a pH more than 4 during more than 90% of the time versus none of the patients of group 1. The plasma concentration versus time curves showed rapid elimination of the drug. The median area under the curve of omeprazole was 0.78 $\mu g \cdot mL^{-1} \cdot h^{-1}$ (range, 0.55–1.64 $\mu g \cdot mL^{-1} \cdot h^{-1}$) and 3.95 $\mu g \cdot mL^{-1} \cdot h^{-1}$ (range, 1.9–4.9 $\mu g \cdot mL^{-1} \cdot h^{-1}$), respectively, in groups 1 and 2 ($P < 0.05$). Systemic clearance was not different between the two groups: median values were 0.68 and 0.42 $L \cdot kg^{-1} \cdot h^{-1}$ ($P = 0.22$).

Conclusions: In critical situations, intravenous administration of omeprazole may be required in infants. The authors demonstrate that the dose of 20 mg/1.73 m^2 is not effective in maintaining 24-hour gastric pH of more than 4 and that a dose of 40 mg/1.73 m^2 is required. ***JPGN 33:144–148, 2001.*** **Key Words:** Omeprazole—Proton pump inhibitors—Intravenous—Infant—Pediatrics. © 2001 Lippincott Williams & Wilkins, Inc.

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 (1). The drug is available for oral and intravenous administration. Intravenous omeprazole has been studied extensively in adult volunteers and in patients treated for gastric acid–related diseases (2–9). In children, most clinical and pharmacologic data were obtained after oral administration, and a mean daily dosage of 1 mg/kg body weight was required to obtain a sustained effectiveness over 24 hours (10–14). When the oral route cannot be used, it is necessary to inhibit acid secretion via intravenous administration. However, only one publication reported the pharmacokinetics of intravenous omeprazole in a limited number of children, but it did not study the effectiveness of the drug (15).

The current study was designed to determine the pharmacokinetics and the optimal dosage of intravenous omeprazole in children younger than 30 months. After randomization, the patients received either 20 mg/1.73 m^2 or 40 mg/1.73 m^2 once daily. A 24-hour intragastric pH study was performed, and the pharmacokinetics of omeprazole was determined after 3 to 5 days of treatment.

PATIENTS AND METHODS

Patients

Nine children (three girls), without severe gastrointestinal bleeding, aged 4.5 to 27 months, requiring intravenous omepra-

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zole were included in the study. They had normal liver and renal functions. None of them received additional drugs known to induce or inhibit the cytochrome P-450 system. Clinical features of these children are presented in Table 1. Review and approval of the study was obtained from the Ethics Committee of Paris-Bichat-Claude Bernard, and informed written consent was obtained from the parents of all our patients.

Study Design

Randomization

Randomization was based on the order of inclusion in the study: the first four patients (patients 1–4) received 20 mg/1.73 m^2, the remaining five (patients 5–9) received 40 mg/1.73 m^2. After enrollment, the children received once daily, at 8 AM, a 1-hour intravenous infusion of either 20 mg/1.73 m^2 or 40 mg/1.73 m^2.

Study drugs

The intravenous formulation of omeprazole consisted of 40 mg lyophilized omeprazole as sodium salt. Immediately before use, the lyophilized drug was mixed thoroughly in an infusion bag containing 100 mL of normal saline. The final solution achieved contained 0.4 mg/mL omeprazole. The corresponding volume was infused over 60 minutes. After 3 to 5 days of treatment, the children were admitted to the Clinical Investigation Unit and a 24-hour intragastric pH and a pharmacokinetic study of omeprazole were performed.

Intragastric pH assessment

At days 3 to 5, after overnight fasting and at least 15 minutes before the infusion of omeprazole, the antimony electrode (Synectics, Stockholm, Sweden) was inserted transnasally and positionned in the body of the stomach. The position of the electrode was determined after localization of the esogastric junction according the Strobel Formula plus 5 cm (16). The electrode was connected to a Digitrapper MarkIII Gold (Synectics). Calibration was made before with standard solutions (pH 1.07 and 7.01). The patients fasted throughout the 24-hour period and were fed parenterally or received intravenous fluids and electrolytes. Tracings were stored on a personal computer and were analyzed using the EsopHogram 5.70 software.

TABLE 1. *Clinical condition of the nine patients*

Patient	Age (months)	Weight (kg)	Condition
1	5.5	6.2	Esophagitis, ultra short bowel
2	21	10.5	Antral ulcer, antral stenosis
3	16	11.8	Antral ulcer, antral stenosis
4	27	10	Duodenal ulcer
5	9	7	Hemoragic gastritis, neonatal leucemia
6	13	7.1	Esophagitis, severe gastroesophageal reflux
7	16	7.8	Esophagitis, esophageal stenosis, repaired esophageal atresia
8	15	9.5	Esophagitis, severe gastroesophageal reflux
9	4.5	5.4	Esophagitis, total colonic aganglionosis with small bowel involvement

Pharmacokinetics and drug assessment

Serial blood samples (1 mL) were collected in heparinized tubes through a venous line (different from the line used for omeprazole infusion) just before (H0), during (H0.75 and H1), and after (H2, H4, H6, H8, H12) omeprazole infusion and immediately centrifuged. Plasma was kept at −20°C until analysis. Plasma concentrations of omeprazole were measured by high-pressure liquid chromatography, following a method adapted from Amantea and Narang (17) with few modifications. Calibration curves in plasma were linear over the range of 10 to 500 ng/mL for omeprazole. The limit of detection was 10 ng/mL.

Data Analysis

Pharmacokinetics

Plasma omeprazole concentrations times profiles were analyzed. The area under the plasma concentration time curves of omeprazole was determined using the trapezoid rule and was extrapolated to infinity by addition of the ratio Ct / λ, where Ct is the last measured plasma concentration and λ is the elimination rate constant. The peak concentration of omeprazole and the time to reach peak concentration were determined graphically. Total systemic clearance was calculated using the ratio of the administered dose over the area under the curve extrapolated to infinity.

Statistics

Mean cumulative percentages of intragastric pH were calculated using the EsopHogram 5.70 software. Median values of gastric pH were calculated from individual pH values using Microsoft Excel software (Microsoft, Redmond, WA). Results were expressed as median and range. Comparisons were by Student's *t*-test or the Mann-Whitney *U* test, with $P < 0.05$ as minimum level of significance.

RESULTS

Intragastric Acidity

The median 24-hour profiles for intragastric pH are shown in Figure 1, and the cumulative relative pH frequency is shown in Figure 2.

The patients treated who received 40 mg/1.73 m^2 had a significantly higher median pH (6.99 vs. 3.35; $P = 0.01$) and a percentage of time over the 23 hours after the

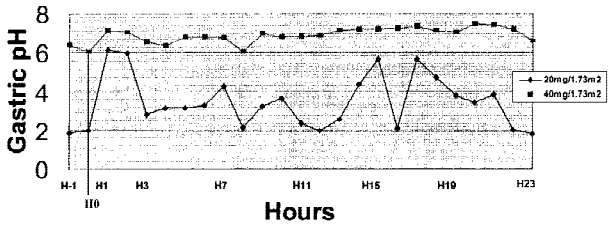

FIG. 1. Median gastric pH in the two groups of children during the 24-hour gastric pH monitoring. Group 1, consisting of the first four patients, received 20 mg/1.73 m^2, and group 2, consisting of the remaining five patients, received 40 mg/1.73 m^2. H-1, 1 hour before infusion of omeprazole; H0, start of infusion of omeprazole; H1 . . . H23, 1 (to 23) hour(s) after start of infusion of omeprazole.

omeprazole infusion with a gastric pH of more than 4 longer (90.6% vs. 44.8%; $P < 0.01$) than the patients who received 20 mg/1.73 m^2. In addition, four of the five children receiving 40 mg/1.73 m^2 were maintained during more than 90% of time with a pH more than 4, whereas no patients receiving 20 mg/1.73 m^2 achieved this (Table 2). Although median pH over 23 hours was significantly lower in patients receiving 20 mg/1.73 m^2, individual responses were variable. As shown in Table 2, patient 4 had a median pH value of 6.4, whereas it was less than 4 in the three other patients of this group.

At steady state, just before the 1-hour infusion of omeprazole, patients receiving 20 mg/1.73 m^2 tended to have a lower median pH than patients treated with 40 mg/1.73 m^2, but the difference was not significant (1.85 vs. 6.4; $P = 0.06$). In the 2 hours after the infusion, a similar major increase in gastric pH values was obtained in both groups: median pH was 6.13 versus 7.14 at H1 and 5.98 versus 7.05 (not significant) at H2 in the low- and high-dose groups, respectively. After H3, median pH was lower in patients receiving 20 mg/1.73 m^2 ($P < 0.01$), and the difference between the two groups persisted until H23 after the infusion of omeprazole.

Pharmacokinetic Parameters

The dose of omeprazole administered in the patients of group 1 was 20 mg/1.73 m^2, the corresponding median dose was 0.56 mg/kg (range, 0.52–0.61 mg/kg). The patients of group 2 received 40 mg/1.73 m^2, corresponding to 1.16 mg/kg (range, 1.09–1.17 mg/kg). The median area under the curve of omeprazole was 0.78 $\mu g \cdot mL^{-1} \cdot h^{-1}$ (range, 0.55–1.64 $\mu g \cdot mL^{-1} \cdot h^{-1}$) and 3.95 $\mu g \cdot mL^{-1} \cdot h^{-1}$(range, 1.9–4.9 $\mu g \cdot mL^{-1} \cdot h^{-1}$) in the low- and high-dose groups, respectively ($P < 0.05$). Systemic clearance was not different between the two groups: median values were 0.68 and 0.42 $L \cdot kg^{-1} \cdot h^{-1}$($P = 0.22$). In the limited number of patients studied, the area under the curve of omeprazole was significantly correlated with the percentage of time with pH more than 4 during 24 hours ($r = 0.67$; $P < 0.05$) but not related to individual median pH values over 24 hours ($P = 0.08$).

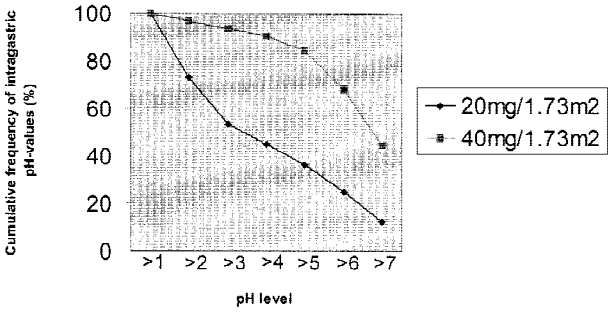

FIG. 2. Mean cumulative percent of intragastric pH in the two groups of children. Group 1 received 20 mg/1.73 m^2, and group 2 received 40 mg/1.73 m^2.

Tolerability

Omeprazole was well tolerated by all the patients, and no significant changes in laboratory variables were found. No adverse effects occurred.

DISCUSSION

Omeprazole inhibits gastric acid secretion by acting selectively on the gastric parietal cell H^+K^+ ATPase (1). In the current study, infants younger than 30 months who required intravenous omeprazole received either 20 or 40 mg/1.73 m^2 and were studied during fasting at steady state. We demonstrated that the dose of 40 mg/1.73 m^2 administered once daily in *fasting patients* was required to achieve a gastric pH more than 4 during more than 90% of the 24-hour period after drug administration.

Omeprazole can be administered orally or intravenously. The pharmacokinetics of omeprazole has been studied in adult healthy volunteers and patients after intravenous and oral administration, and reviews are available (18,19). In children, the pharmacokinetics of omeprazole was, in almost all cases, studied after oral administration (20–22). A single previous study was undertaken in patients aged 0.3 to 19 years with intravenous omeprazole (15). In the current study, the patients were all less that 30 months of age, but the pharmacokinetic parameters of omeprazole were similar to those reported in studies of adults and older children.

In adults, the effect of omeprazole on 24-hour intragastric acidity was reported to be twice as effective after intravenous than after oral administration, 10 mg administered intravenously being equivalent to 20 mg administered orally in duodenal ulcer patients (5) or healthy subjects (6). When measured by pentagastrin-stimulated acid secretion in duodenal ulcer patients, the effect of 20 mg administered orally was also as potent as 10 mg administered intravenously (7). In adults, the dose of 40 mg intravenous omeprazole was found optimal to achieve a rapid and complete inhibition of gastric acid

TABLE 2. *Pharmacokinetics and gastric pH in the nine patients*

Patient	Dose (mg/1.73 m^2)	Dose (mg/kg)	AUC ($\mu g \cdot h/ml$)	Clearance ($L \cdot kg^{-1} \cdot h^{-1}$)	Median gastric pH	Time above pH 4 (%)
1	19.92	0.61	1.64	0.37	3.57	53.1
2	20.18	0.53	0.71	0.75	3.04	44.7
3	19.91	0.52	0.85	0.60	1.8	16.1
4	20.18	0.56	0.55	1.01	6.4	65.2
5	39.54	1.14	1.43	0.80	7.23	99.8
6	39.89	1.17	1.90	0.61	5.99	58.9
7	39.92	1.15	4.9	0.23	6.95	100
8	39.98	1.09	3.78	0.28	5.58	94.5
9	40.37	1.30	7.71	0.16	7.39	100

secretion, this dosage inhibiting 95% of pentagastrin acid output after the first dose and 100% after the fifth dose (5,6). In our study, the dose of 20 mg/1.73 m^2 (0.56 mg/kg) intravenously was not sufficient to inhibit gastric acid secretion, with a clear-cut return of acidity 4 hours after intravenous dosing. This suggests that the effect of 20 mg/1.73 m^2 omeprazole administered once daily is not long enough to create a complete inhibition of the H^+K^+ ATPase over more than 4 hours. The dose of 40 mg/1.73 m^2 (1.17 mg/kg), higher than the equivalent-recommended oral dose in children, was required to achieve gastric pH more than 4 during more than 90% of the 24-hour period after intravenous omeprazole administration. The pharmacokinetics of intravenous omeprazole were similar to previous data and could not explain such results. The fasting condition in which the gastric pH monitoring was performed may play a role, because this could modify the access of the drug to the H^+K^+ ATPase. Indeed, omeprazole is active in the luminal side of the secretory membrane of the gastric parietal cells. After formation of a sulfonamide form, omeprazole reacts with SH-groups, forming a covalent disulfide bond irreversibly inhibiting the H^+K^+ ATPase. To be effective, this requires the exteriorization of the H^+K^+ ATPase, best obtained after a meal (1). Therefore, it is possible that in the fasting patients that we studied, the H^+K^+ ATPase probably was not exteriorized completely, suggesting that, as in adults, parietal cell activity greatly influences the antisecretory effect of omeprazole. In addition, the rate of recycling proton pumps may be different in infants compared with children and adults, but this would be very difficult to investigate.

In the current short-term study, we did not report any adverse effect even in children who received the higher dose. It should be underlined that the excess acid suppression during prolonged periods has been associated with bacterial overgrowth in adults (23) and in neonates (24). This suggests that the intravenous administration of omeprazole, which profoundly inhibits the gastric acid secretion, should be the shortest, with oral administration as soon as possible.

In some critical situations such as acute digestive bleeding, a rapid antisecretory effect may be required. Ranitidine and other H2-blockers have been used successfully in pediatric patients with a clearly rapid onset of efficacy (25). However, this effect is short lived, and the gastric pH falls within 24 hours, despite continuous infusion (26). In adults, the inhibitory effect of omeprazole on gastric acidity was much more rapid after the first administration of 40 mg intravenously compared with 20 mg orally, whereas the effect of the two routes were similar after 5 days of treatment (4–7). In addition, the benefit of a loading dose was demonstrated (27). Although the delay for efficacy was not investigated in the current study, we suggest using a loading dose of 40 mg/1.73 m^2, repeated after 12 hours to achieve a rapid antisecretory effect in similar critical situations in pediatric patients. Despite omeprazole interaction with the cytochrome P-450 system, no clinically important interactions have been observed between proton-pump inhibitors and other drugs (1,28). This suggests that in critical situations, intravenous omeprazole may be administered safely for short-term treatment when the oral route is impossible.

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