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 m2, and group 2, consisting of the following five patients, received 40 mg/1.73 m2. 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 m2 (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 g·m L−1·h−1 (range, 0.55–1.64 g·m L−1·h−1) and 3.95 g·m L−1·h−1 (range, 1.9–4.9 g·m L−1·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·kg−1·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 m2 is not effective in maintaining 24-hour gastric pH of more than 4 and that a dose of 40 mg/1.73 m2 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 m2 or 40 mg/1.73 m2 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-
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 m², the remaining five (patients 5–9) received 40 mg/1.73 m². After enrollment, the children received once daily, at 8 AM, a 1-hour intravenous infusion of either 20 mg/1.73 m² or 40 mg/1.73 m².

**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 positioned in the body of the stomach. The position of the electrode was determined after localization of the esogastric junction according to 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.

**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 / H9261, 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 m² 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

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**TABLE 1. Clinical condition of the nine patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (months)</th>
<th>Weight (kg)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>6.2</td>
<td>Esophagitis, ultra short bowel</td>
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<tr>
<td>2</td>
<td>21</td>
<td>10.5</td>
<td>Antral ulcer, antral stenosis</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>11.8</td>
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</tr>
<tr>
<td>4</td>
<td>27</td>
<td>10</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>7</td>
<td>Hemoragic gastritis, neonatal leukemia</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>7.1</td>
<td>Esophagitis, severe gastroesophageal reflux</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>7.8</td>
<td>Esophagitis, esophageal stenosis, repaired esophageal atresia</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>9.5</td>
<td>Esophagitis, severe gastroesophageal reflux</td>
</tr>
<tr>
<td>9</td>
<td>4.5</td>
<td>5.4</td>
<td>Esophagitis, total colonic aganglionosis with small bowel involvement</td>
</tr>
</tbody>
</table>
The dose of omeprazole administered in the patients of group 1 was 20 mg/1.73 m², the corresponding median pH was significantly lower in patients receiving 20 mg/1.73 m², but the difference was not significant (1.85 vs. 6.4; \( P < 0.01 \)). 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 m² (\( P < 0.01 \)), 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 m², the corresponding 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 m² (\( P < 0.01 \)), and the difference between the two groups persisted until H23 after the infusion of omeprazole.

**DISCUSSION**

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

**Omeprazole**

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 (\( P = 0.08 \)).

Omeprazole inhibits gastric acid secretion by acting selectively on the gastric parietal cell H⁺K⁺ ATPase (1).

Omeprazole was well tolerated by all the patients, and no significant changes in laboratory variables were found. No adverse effects occurred.
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 m² (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 m² 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/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 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 m², 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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REFERENCES


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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg/1.73 m²)</th>
<th>Dose (mg/kg)</th>
<th>AUC (µg·h/ml)</th>
<th>Clearance (L·kg⁻¹·h⁻¹)</th>
<th>Median gastric pH</th>
<th>Time above pH 4 (%)</th>
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<tr>
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<td>1.15</td>
<td>4.9</td>
<td>0.23</td>
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