Pharmacokinetics, pharmacodynamics, and safety of esomeprazole injection/infusion in healthy Chinese volunteers: A five-way crossover study

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Abstract

Background: Esomeprazole provides effective and long lasting inhibition of gastric acid secretion. However, the pharmacokinetics and pharmacodynamics of intravenous esomeprazole in the Chinese population remain unclear.

Aim: To compare the pharmacokinetics and pharmacodynamics of intravenous esomeprazole (injection and infusion) and their clinical safety and tolerability in healthy Chinese subjects.

Methods: A randomized, single-center, open-label, five-way crossover study was conducted in 20 healthy volunteers. CYP2C19 metabolizer genotype and Helicobacter pylori status were examined. Five dosing regimens were used: single 40 mg injection, 40 mg infusion every 12 h, 40 mg infusion followed by continuous infusion at 8 mg/h, 80 mg infusion followed by continuous infusion at 4 or 8 mg/h. Intragastric pH was recorded within 24 h. Plasma concentration-time curve, maximum plasma concentration (Cmax), steady state concentration, and total plasma clearance were determined. Adverse events were also recorded.

Results: Continuous infusion resulted in a higher mean area under the curve and Cmax than injection. There were no significant differences among the four infusion groups in terms of percentages of time at pH > 4, > 5, > 6, > 7 within 24 h and pH > 6 within the first 3 h. There were no significant differences in pharmacokinetic or pH values among variants of CYP2C19 genotype. The pH value within 24 h was unaffected by H. pylori infection in subjects with continuous infusion.

Conclusions: Esomeprazole administered by infusion produces better pharmacokinetic and intragastric pH profiles compared with those by injection. The optimal administration schedule for esomeprazole in Chinese subjects is infusion with 40 mg/12 h.

Introduction

Proton-pump inhibitors (PPIs) are the most effective agents for suppressing gastric acid secretion and are the drugs of choice for the treatment of hyper-gastric acid disorders. The amount of time that intragastric pH is > 4.0 is frequently used as a parameter to evaluate the pharmacodynamics and clinical effects of treatment with PPIs in patients with acid-related disease.1–3

The PPI esomeprazole, the S-isomer of omeprazole, has pharmacological advantages over the racemic compound. Esomeprazole provides a more profound and longer lasting inhibition of gastric acid secretion during a 24-h period than any other PPIs.2,4 Oral esomeprazole is widely available and is prescribed for the healing and maintenance treatment of gastroesophageal reflux disease (GERD), peptic ulcers, and eradication of Helicobacter pylori infection, when combined with antibiotics.

An intravenous (i.v.) formulation of esomeprazole has been developed for patients unable to take the oral formulation, or for situations where oral administration would be inappropriate. Several earlier studies investigated the pharmacodynamic effects of i.v. esomeprazole. Both a 30-min i.v. infusion and a 3-min injection of 40 mg esomeprazole were shown to provide similar levels of gastric acid suppression in healthy volunteers.5 Additionally, both the i.v and oral administration of 40 mg of esomeprazole resulted in similar control of intragastric pH.6 The current study compared the pharmacokinetics and pharmacodynamics of esomeprazole infusion and injection in healthy Chinese volunteers, and investigated its clinical safety and tolerability using a five-way crossover design.
Materials and methods

A randomized, single-center, open-label, five-way crossover study was conducted at Peking Union Medical College Hospital in China, in accordance with the ethical principles guidelines. The study was approved by the local institutional review board at Peking Union Medical College Hospital. All subjects provided signed informed consent. Using a validated computer program, a treatment allocation list (randomized list) was generated to assign subjects to a treatment group. The sequence of the treatment was determined using a balanced Latin square.

The primary variable was the amount of time with intragastric pH > 4 during the 24-h study period on day 5 following esomeprazole injection or infusion.

Subjects. Healthy volunteers aged 24–41 years were eligible for this study. Inclusion criteria were: body mass index of 20–24.7 kg/m²; body weight 48–74 kg; clinically normal laboratory values and physical findings as judged by the investigators; H. pylori status were detected by 13C-urea breath test; CYP2C19 metabolizer status were assessed by genotyping; and intragastric pH > 4 for < 30% of the time during a baseline 24-h pH were recorded.

Exclusion criteria were: any significant clinical illness within the 2 weeks preceding the first dose of study drug; history of cardiac, renal, hepatic, neurological or gastrointestinal diseases, or severe allergy; pregnancy, lactation, or childbearing potential (unless taking necessary precautions against pregnancy); the use of prescribed medication within the 2 weeks preceding the first dose of study drug; the use of any clinical trial drug in the 8 weeks preceding the study; moderate to heavy smoking; or a history of drug addiction or alcohol abuse.

Procedure. Forty milligram esomeprazole powder (40 mg as esomeprazole sodium 42.5 mg, batch number D9615L0007-001 and D9615L0007-002, AstraZeneca AB, Sweden) was reconstituted with 5 mL saline solution (9 mg/mL NaCl) to produce 8 mg/mL esomeprazole solution. In the case of i.v. infusion, 5 mL of the esomeprazole solution was further diluted with saline to a final volume of 100 mL, and the solution was infused by infusion pump about 30 min. Five i.v. dosing regimens were designed: (i) 40 mg esomeprazole (corresponding to 5 mL esomeprazole solution) was slowly i.v. injected for 3 min; (ii) 40 mg esomeprazole infusion for 30 min every 12 h; (iii) 40 mg esomeprazole infusion for 30 min and followed by continuous infusion at 8 mg/h; (iv) 80 mg esomeprazole infusion for 30 min and followed by continuous infusion at 4 mg/h; and (v) 80 mg esomeprazole infusion for 30 min and followed by continuous infusion at 8 mg/h. Subjects were randomized to receive one of the five regimens and were observed for 24 h. After a washout period of at least 6 days, subjects were crossed over to receive another treatment.

Observation items

Intragastric pH recording. In each study, intragastric pH recording was measured for 24 h at baseline (≤ 14 days before the first treatment period) and 24 h during treatment periods. A calibrated pH microelectrode (Digitrapper MKIII, Medtronic Inc., Copenhagen, Denmark) was placed approximately 10 cm below the lower esophageal sphincter. Each study subject was assigned their own electrode, which was placed in the same position during all five pH recordings throughout the study. pH measurements were taken every 10 s using a Medical Measurement System (Orion pH-data logger; Enschede, the Netherlands). The percentages of time with intragastric pH > 7, > 6, > 5, and > 4 over 24 h were recorded. Time to pH > 6 maintained for more than 1 h and the percentage of time with intragastric pH > 6 during the first 3 h after start of dose were also recorded.

Pharmacokinetics. To determine the plasma concentration of esomeprazole, blood samples (5 mL) were taken before and after study drug administration at 10, 20, 30, 45, 60, 75, 90, 105, 120 min, and 3, 4, 5, 6, 8, 10, 12, and 24 h. The plasma concentrations of esomeprazole were determined by a validated liquid chromatography-mass spectrometry/mass spectrometry method at Clinical Pharmacology Research Center Bioassay Lab, Peking Union Medical College Hospital, Beijing. The pharmacokinetic variables of area under the plasma concentration-time curve (AUC), maximum plasma concentration (Cmax), steady state concentration (Css), and total plasma clearance (CL) were calculated.

Safety evaluation. Blood and urine samples were taken at a pre-entry visit and a follow-up visit and subjected to standard laboratory tests. Physical examinations, blood pressure and pulse measurements, and electrocardiograms were carried out at pre-entry and each day during the 6-day washout period. Adverse events and serious adverse events were recorded throughout the study period, from initial administration until the end of the study.

P450 enzyme genotyping and H. pylori detection. The P450 CYP2C19 genotype was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. For exon 5 of CYP2C19 gene, the forward primer (m1a) was 5′-AATTACACAGAGGTTGGC-3′, the reverse primer(m1b) was 5′-TATCACCTTTCATATAAAAGCAAG-3′; for exon 4, the forward primer (m2a) was 5′-AAATTGTGTTCCAATCATTTAGCT-3′, the reverse primer (m2b) was 5′-ACTTCAGGGCTTGGTGCTAAA-3′. Two restriction endonuclease of Smal and BamHI for CYP2C19m1 and CYP2C19m2 were done to digest polymerase chain reaction (PCR) products. Based on PCR results, subjects with wild-type alleles in both exons 4 and 5 of the CYP2C19 gene were classified as homozygous extensive metabolizers (homo-EMs); subjects with only one mutated allele in either exon 4 or exon 5 were heterozygous extensive metabolizers (hetero-EMs); subjects with two mutated alleles in each of exons 4 and 5 were poor metabolizers (PMs). The PM phenotype includes CYP2C19m1/m1, CYP2C19m1/m2, or CYP2C19m2/m2. The extensive metabolizers (EM) phenotype includes homozygous EM (wide type, wt/wt) and heterozygous EM (wt/m1, wt/m2).

The 13C-urea breath test was performed to detect H. pylori in all subjects. In brief, a baseline breath sample was collected after overnight fasting to ensure that the system was free of radioactivity. Subjects then immediately ingested a tablet containing...
\( ^{13}\)C-urea with water. After 30 min, a breath sample was collected without a mouthwash. Breath samples were analyzed by mass spectrometry.

**Statistical analysis.** Pharmacodynamic and pharmacokinetic variables were analyzed. A mixed-model analysis of variance (ANOVA) with fixed effects for period, sequence, and treatment, and a random effect was used to analyze the pharmacokinetic variables AUC, C\(_{\text{max}}\), C\(_{\text{ss}}\), and C\(_{\text{L}}\) for subjects within sequences. Geometric means and two-sided 95% confidence intervals (CIs) were calculated for all variables for each treatment.

A mixed-model ANOVA was used with fixed effects for period, sequence, and treatment, and a random effect for subjects with intragastric pH value during the 24 h following esomeprazole administration. The mean of each treatment and the mean treatment difference were calculated with two-sided 95% CIs. The mean AUC value in the group receiving 40 mg i.v. followed by 8 mg/h infusion was slightly higher than that in the group receiving 80 mg i.v. followed by 4 mg/h infusion.

**pH value detection.** Median intragastric pH traces within 24 h for both groups are presented in Figures 2 and 3. Except for the 40 mg injection group, there were no significant differences between the infusion groups. The percentages of time at pH > 4, > 5, > 6, and > 7 within 24 h and the percentage of time at pH > 6 within the first 3 h were calculated (Table 3 and Fig. 4). The percentage of time at pH > 5 was higher in the group receiving 40 mg injection followed by 8 mg/h infusion as compared with other groups.

### Results

**Subjects.** Twenty healthy subjects were enrolled in this study. Their baseline characteristics are shown in Table 1. The average age of the subjects was 33.3 years. The ratio of males to females was 14:6. *H. pylori* were detected in all subjects, 9 subjects were positive, and the others were negative for *H. pylori*. In CYP2C19 metabolizer phenotype, 11 were heterozygote-EM (55%), seven were homozygote-EM (35%), and two were PM (10%).

**Pharmacokinetic evaluation.** The geometric means (95% CI) of the pharmacokinetic parameters in each group are summarized in Table 2. The plasma concentration-time curves in the 24 h following i.v. administration by each method are shown in Figure 1. The plasma concentration reached a peak value within 30 min in all groups after the bolus dosage. Following 80 mg i.v., the mean AUC and C\(_{\text{max}}\) were higher with continuous 8 mg/h infusion as compared with 4 mg/h infusion. The mean AUC value in the group receiving 40 mg i.v. followed by 8 mg/h infusion was slightly higher than that in the group receiving 80 mg i.v. followed by 4 mg/h infusion.

### Table 1 Baseline characteristics of subjects in this study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>33.3</td>
<td>163.5</td>
<td>59.5</td>
<td>22.2</td>
</tr>
<tr>
<td>SD</td>
<td>3.8</td>
<td>6.2</td>
<td>6.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Min</td>
<td>24.0</td>
<td>153.0</td>
<td>48.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Median</td>
<td>34.0</td>
<td>163.5</td>
<td>61.0</td>
<td>22.1</td>
</tr>
<tr>
<td>Max</td>
<td>41.0</td>
<td>173.0</td>
<td>74.0</td>
<td>24.7</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.

### Table 2 Geometric means (95% CI) for pharmacokinetic parameters in each dosage regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>40 mg Inf</th>
<th>40 mg bid</th>
<th>Dosage regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0–24 ((\mu\text{mol}^*\text{h/L}))</td>
<td>14.6 (12.5–17.1)</td>
<td>14.3 (11.9–17.2)</td>
<td>96.0 (84.6–108.9)</td>
</tr>
<tr>
<td>C(_{\text{max}}) ((\mu\text{mol/L}))</td>
<td>10.8 (9.9–11.8)</td>
<td>9.1 (8.1–10.3)</td>
<td>9.5 (8.5–10.6)</td>
</tr>
<tr>
<td>C(_{\text{ss}}) ((\mu\text{mol/L}))</td>
<td>NA</td>
<td>NA</td>
<td>3.5 (3.1–4.0)</td>
</tr>
<tr>
<td>C(_{\text{L}}) (L/h)</td>
<td>NA</td>
<td>NA</td>
<td>6.6 (5.8–7.6)</td>
</tr>
</tbody>
</table>

\(^{1}\)AUC 0–12.

bid, twice daily; inj, injection; inf, infusion; NA, not assessed.
**pH value and H. pylori status.** The pH value versus *H. pylori* status was analyzed for each group. The median intragastric pH profiles for each group were similar in *H. pylori*-positive subjects. However, the pH value was obviously decreased after 12 h in the 40 mg injection group in *H. pylori*-negative subjects. Further analysis revealed that dosage regimens with bolus alone were affected by *H. pylori* status, but the pH value within 24 h was unaffected by *H. pylori* status following continuous infusion (Fig. 4).

**CYP2C19 metabolizer genotype and the association with the pharmacokinetic, pH values.** According to the drug-metabolizing phenotype of S-mephenytoin 4'-hydroxylase (S-MP, cytochrome P450 enzyme CYP2C19), there are EM and PM. Genotyping analysis of 20 subjects for Cyp2C19 was done by PCR-RFLP. Seven subjects showed homozygous-EM (Fig. 5a); 11 subjects showed heterozygous EM (Fig. 5b); and 2 subjects were PM (Fig. 5c).

The pharmacokinetic results were analyzed according to CYP2C19 metabolizer status. The mean AUC value differed slightly between homo-EM, and hetero-EM and PM for all groups. Hetero-EM and PM individuals had higher AUC values. However, the mean plasma concentration-time curves were unaffected by CYP2C19 genotype (data not shown).

**pH values** were also analyzed according to CYP2C19 metabolizer status in each group. pH parameters showed slight differences between homo-EM and hetero-EM/PM individuals for all five dosing groups, with hetero-EM/PM subjects having slightly higher pH values (data not shown).

**Safety evaluation.** The drug was well tolerated by subjects in all groups. Most adverse events were of mild to moderate intensity, and no serious adverse events were reported. There were no clinically significant changes in all subjects of the physical examination, laboratory test, and electrocardiogram reports before and after the administration.
Discussion

This study, to the best of our knowledge, represents the first investigation on pharmacokinetics, pharmacodynamics, and safety of esomeprazole injection/infusion in healthy Chinese subjects using a five-way crossover design. The study aimed to compare the difference in plasma concentrations and intragastric acid control between different doses of esomeprazole administered by injection or infusion. The results demonstrated that esomeprazole infusion produced more stable plasma concentrations within 24 h as compared with esomeprazole injection. Following a single injection of 40 mg, the plasma concentration was only maintained for 12 h because of the short half-life of esomeprazole (1.2 h). The amount of time at intragastric pH > 4 was similar for the infusion groups within 24 h, but the pH value became unstable and fell below 4 after 15 h in the injection group. These results thus demonstrate that administration of esomeprazole by infusion is the optimal way of controlling intragastric pH in a healthy Chinese population.

Table 3 Mean (95% CI) of pH variables according to dosage regimens

<table>
<thead>
<tr>
<th>Dosage regimen</th>
<th>24-h period</th>
<th>Percentage of time with</th>
<th>0–3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH &gt; 4</td>
<td>pH &gt; 6</td>
<td>pH &gt; 7</td>
</tr>
<tr>
<td>40 mg (3 min) od</td>
<td>77.8 (73.4–82.2)</td>
<td>41.1 (33.6–48.6)</td>
<td>9.3 (3.6–14.9)</td>
</tr>
<tr>
<td>40 mg (0.5 h) bid</td>
<td>91.4 (87.1–95.7)</td>
<td>49.4 (42.1–56.8)</td>
<td>16.0 (10.4 – –21.6)</td>
</tr>
<tr>
<td>40 mg + 8 mg/h</td>
<td>95.4 (91.0–99.8)</td>
<td>57.2 (49.7 – –64.7)</td>
<td>16.7 (11.0–22.4)</td>
</tr>
<tr>
<td>80 mg + 4 mg/h</td>
<td>95.5 (91.3–99.8)</td>
<td>49.9 (42.6–57.1)</td>
<td>15.0 (9.4–20.5)</td>
</tr>
<tr>
<td>80 mg + 8 mg/h</td>
<td>95.7 (91.4–100)</td>
<td>53.0 (45.6–60.3)</td>
<td>15.1 (9.5–20.7)</td>
</tr>
</tbody>
</table>

†Significant difference versus bolus + continuous infusion. od, once daily; bid, twice daily.
‡Significant difference versus 40 mg (3 min) od.

Figure 4 Median intragastric pH profiles by H. pylori status in 40 mg injection and 40 mg infusion bid groups (a). The pH value was not maintained after 12 h in H. pylori-negative subjects in the injection group. The pH values were maintained at similar levels in groups receiving a bolus dose followed by a continuous infusion (b).

Figure 5 Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis for CYP2C19 genotype. For M1, only one band 169 bp shows the genotype CYP2C19m1/m1, two bands (120 bp, 49 bp) for CYP2C19wt/wt, and three bands (169 bp, 120 bp, and 49 bp) for CYP2C19wt/m1. For M2, only one band 271 bp shows the genotype CYP2C19m2/m2, two bands (175 bp, 96 bp) for CYP2C19wt/wt, and three bands (271 bp, 175 bp, and 96 bp) for CYP2C19wt/m2. (a) homozygous-EM phenotype; (b) heterozygous-EM phenotype; (c) PM phenotype. D represented digested PCR products and N represented no-digested PCR products.
An esomeprazole i.v. dosage regimen of 80 mg + 8 mg/h appeared to be optimal for acid suppression in healthy subjects in Western countries,9 while esomeprazole 40 mg twice a day was significantly more effective in controlling intragastric pH in patients with Barrett’s esophagus.10 Four esomeprazole infusion schedules were used in the current study. Higher Cmax and AUC values were associated with continuous infusion, and AUC was affected by continuous infusion dosage, rather than by the initial dosage. Esomeprazole administered as a 30-min infusion twice within 24 h resulted in a similar level of intragastric acid control compared with continuous infusion over 24 h. In addition, no significant differences in the percentage of time at pH > 5, 6, or 7 were detected between any of the infusion groups. The percentage of pH value > 6 in the first 3 h was also similar in all four infusion groups. A previous study reported that i.v. esomeprazole 40 mg provided similarly potent acid control when administered by either injection or infusion.11 This apparent discrepancy may be because this previous study lasted for 10 days, while the current study observed changes within 24 h.

The results of the present study showed that esomeprazole 40 mg infusion twice a day resulted in better pharmacokinetic and pharmacodynamic profiles than a 40 mg injection once a day, and was similar to a 4 mg/h or 8 mg/h continuous infusion. Esomeprazole 40 mg infusion every 12 h represents the optimal method of administration for the Chinese population in terms of the cost of medicine and the convenience of treatment.

Esomeprazole is eliminated by hepatic metabolism mediated by the CYP2C19 enzymes.12,13 The CYP2C19 genotype affects both first-pass and systemic metabolism. Several clinical studies have shown that the CYP2C19 genotype can influence the effects of esomeprazole on H. pylori eradication and GERD treatment.14 A previous study demonstrated that CYP2C19 genetic polymorphisms affected the pharmacokinetics and pharmacodynamics of omeprazole in Chinese population.15 Most individuals in the current study were heterozygote-EM type. However, CYP2C19 genotype had no apparent effect on AUC value or intragastric acid control in any group. The discrepancy between our results and those of the previous studies may be due to fewer subjects in the current study. Future studies to investigate the relationship between hepatic P450 enzyme genotype and esomeprazole effects in the Chinese population should therefore include more subjects.

H. pylori infection is known to be the main etiology of gastritis and peptic ulcers. The current study demonstrated a relationship between H. pylori infection and the acid-controlling effect of esomeprazole. Esomeprazole injection could maintain the pH value > 4 after 15 h in H. pylori-infected individuals, but this effect was reduced in H. pylori-negative subjects. The percentage of time at pH value was also slightly affected by H. pylori status in the 40 mg two infusion group, compared with the continuous infusion groups. Few studies have investigated the effects of H. pylori infection on the control of intragastric pH by esomeprazole. However, a recent study of PPI treatment of GERD showed that patients with GERD needed a 1.9-fold higher dose, and H. pylori-positive individuals needed only about 20% of the dose to achieve a given increase in mean 24-h intragastric pH.16 The results of this study imply that H. pylori infection may affect the pharmacodynamics of PPI. Further studies are required to verify this effect.

In conclusion, esomeprazole infusion is more effective than injection in terms of pharmacokinetic values and intragastric pH profiles. Furthermore, administration by infusion was unaffected by H. pylori infection status. A dosage schedule of 40 mg per 12 h thus represents the optimal esomeprazole administration schedule in Chinese subjects.

References
