Population Pharmacokinetics and Proton Pump Inhibitory Effects of Intravenous Lansoprazole in Healthy Japanese Males

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A total of 56 healthy Japanese males were enrolled in single- or multiple- dose pharmacokinetic trials of intravenous lansoprazole administration. The population pharmacokinetics of the drug was evaluated using nonlinear mixed effects model (NONMEM) software. In addition, the effect of CYP2C19 polymorphism on proton pump inhibition by lansoprazole was investigated using 24-h intragastric pH monitoring in the 32 subjects. Time course of serum lansoprazole concentration following intravenous short infusion was well described by a 2-compartment model. The mean volume of the central and peripheral compartments was 0.110 and 0.201 l/kg, respectively. The mean inter-compartment clearance was estimated to be 0.0882/l/h/kg. The population mean value of systemic clearance in the homoEM (CYP2C19*1/*1), heteroEM (CYP2C19*1/*2 and *1/*3), and PM (CYP2C19*2/*2, *2/*3, and *3/*3) groups was 0.179, 0.109, and 0.038 l/h/kg, respectively. The mean intragastric pH following twice-daily doses of 30 mg lansoprazole was approximately 6, 5, and 4 in the PM, heteroEM, and homoEM groups, respectively. These findings indicate that large interindividual variability exists in the pharmacokinetics of intravenously administered lansoprazole, but that twice-daily infusion of a 30 mg dose leads to significant and sustained proton pump inhibition, even in the homoEM group, despite the short elimination half-life of the drug.

Key words lansoprazole; population pharmacokinetics; healthy Japanese subject; CYP2C19

Upper gastrointestinal bleeding is one of the common causes of emergency hospital admission in Japan, and it possibly results in life-threatening massive hemorrhage. Endoscopic clipping of the bleeding vessel is usually effective for treating gastrointestinal hemorrhage, but rebleeding occurs in 15 to 20% of patients.1) Higher intragastric pH promotes platelet aggregation, and the inhibition of gastric acid secretion to maintain neutral pH may stabilize clots and prevent recurrent bleeding.2) Intravenous administration of histamine H2-receptor antagonists has been widely used for the management of gastrointestinal hemorrhage, particularly after endoscopic clipping. However, gastric acid secretion is not solely regulated by the histamine H2-receptor, and tolerance to the antisecretory activity of H2-receptor antagonists frequently develops during infusion over 72-h periods, leading to a loss of pH control.3,4) Meta-analyses have also suggested that H2-receptor antagonists only have a weak beneficial effect.5) On the other hand, proton-pump inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system located on the secretory surface of gastric parietal cells.5—7) High doses of PPIs maintain the intragastric pH at a nearly neutral level, and inhibit acid production more effectively than an infusion of H2-receptor antagonists.3,8) Therefore, high-dose intravenous PPI therapy is theoretically superior to intravenous H2-receptor antagonist therapy for the prevention of recurrent bleeding. In fact, several studies have indicated that intravenous administration of PPIs is effective for the treatment of patients with gastrointestinal bleeding.1,4,9,10)

It has been reported that PPIs (omeprazole and lansoprazole) are mainly metabolized by cytochrome P450 (CYP) 2C19.1,11,12) The genetic polymorphisms of CYP2C19 have been observed in Asian populations, and three polymorphic alleles, CYP2C19*1 (wild-type), CYP2C19*2, and CYP2C19*3, have been identified among Japanese.13) CYP2C19*2 causes a splicing defect in exon 5, and CYP2C19*3 creates a premature stop codon in exon 4.13) Therefore, these mutations lead to the complete loss of the enzymatic activity of CYP2C19. The allele frequencies of CYP2C19*2 and CYP2C19*3 among Japanese are reported to be 28.7% and 13.2%, respectively.14) It has been reported that genetic polymorphisms of CYP2C19 are responsible for the large interindividual variability in the pharmacokinetics of orally administered PPIs in Japanese populations.15,16)

Recently, a new preparation for intravenous injection of lansoprazole was developed in Japan. In the present study, we evaluated the population pharmacokinetics of intravenously administered lansoprazole in healthy Japanese subjects using a nonlinear mixed effects model (NONMEM) program. We also evaluated the effect of CYP2C19 polymorphisms on proton pump inhibition by intravenously administered lansoprazole.

MATERIALS AND METHODS

Subjects A total of 56 healthy Japanese adult male volunteers participated in this study. All of the subjects were confirmed to be healthy on the basis of their medical history, physical findings, laboratory studies, and 12-lead electrocardiogram. The subjects ranged in age from 20 to 34 (mean ± S.D.: 24.0 ± 4.0) years old, and their weight (± S.D.) was 61.8 ± 6.0 kg. The subjects were classified into three groups.

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according to their CYP2C19 genotype. The CYP2C19*1 (wild type) allele and two defective allelic variants, CYP2C19*2 and CYP2C19*3, were determined using the allele specific primer polymerase chain reaction (PCR) method (SNP Typing Kit; Toyobo, Osaka, Japan) or the PCR-restriction fragment length polymorphism method.13,17 Sixteen subjects homozygous for the CYP2C19*1 allele were defined as extensive metabolizers, and were designated as homoEM group. Thirty-two subjects heterozygous for mutant alleles (CYP2C19*1/*2 and *1/*3) were defined as intermediate metabolizers, and were designated as heteroEM group. Finally, 8 subjects homozygous for mutant alleles (CYP2C19*2/*2, *2/*3, and *3/*3) were defined as poor metabolizers, and were designated as PM group. All subjects gave written informed consent to participate in this study, which was approved by the institutional review boards of Ohsaki Clinic (Tokyo, Japan), Sekino Clinical Pharmacology Clinic (Tokyo, Japan), and Kyushu Clinical Pharmacology Research Clinic (Fukuoka, Japan).

**Study Design**

Serum lansoprazole concentration data for population pharmacokinetic analysis were obtained during the single and multiple dose trials. Briefly, all 56 subjects received 30 mg lansoprazole by intravenous drip infusion over 30 min, and blood samples were collected periodically for the determination of serum lansoprazole concentration over 12 h after the dose (see Fig. 1A). To evaluate the constancy of pharmacokinetics, 16 (8 PMs, 7 heteroEMs, and 1 homoEM) of 56 subjects received twice-daily drip infusions of 30 mg lansoprazole repetitively for 5 d, and blood samples were collected periodically on day 5 (see Fig. 1B). To assess the linearity of the pharmacokinetics of lansoprazole, 8 (3 heteroEMs, and 5 homoEMs) of 56 subjects received 30 mg of lansoprazole as an intravenous bolus injection. Furthermore, 8 (5 heteroEMs, and 3 homoEMs) of 56 subjects received a single dose of 15 mg lansoprazole by drip infusion over 30 min. Blood samples were collected periodically over 12 h after the dose (see Figs. 1C, D).

Intragastric pH monitoring was performed in 32 of 56 subjects to evaluate the effect of CYP2C19 genotype on proton pump inhibition by 30 mg lansoprazole. In the 16 subjects (8 PMs, 7 heteroEMs, and 1 homoEM), who received twice-daily drip infusions of 30 mg lansoprazole repetitively for 5 d, 24-h intragastric pH monitoring was performed on day 1 and day 5. A microglass electrode (CM-181; Chemical Instruments) was introduced per-nasally into the body of the stomach under fluoroscopic guidance. Intragastric pH data were recorded with a one-channel pH meter (101ZG; Chemical Instruments, Tokyo, Japan). For comparison, those 16 subjects also received twice-daily drip infusions of 75 mg roxatidine acetate repetitively for 5 d, and 24-h intragastric pH monitoring was performed on day 1 and day 5 as described above. In additional 16 subjects (8 heteroEMs, and 8 homoEMs), 30 mg lansoprazole was infused intravenously two times a day at a 12-h interval, and 24-h intragastric pH monitoring was performed on the day (day 1), as described above.

**Assay of Lansoprazole**

The serum concentration of lansoprazole was determined by the HPLC method reported by Aoki et al.18 Briefly, lansoprazole was extracted from 500 μl of human serum with 3 ml of a mixture of diethyl ether and dichloromethane (7:3, v/v). The extract was evaporated to dryness under a stream of nitrogen gas, and then the residue was dissolved in 300 μl of a mixture of water and acetonitrile (7:3, v/v). A 100 μl aliquot of the solution was injected onto a TSK-GEL ODS 120T column (5 μm, 250 mm×4.6 mm I.D.). The mobile phase consisted water/acetonitrile/n-octylamine (620:380:1, v/v/v, pH 7). Lansoprazole was detected at 285 nm with an UV detector, and its concentration was determined from the ratio of peak height of the drug to that of isobutyl p-hydroxybenzoate (an internal standard). Linearity was obtained between 5 ng/ml and 2000 ng/ml, and the lower limit of quantification was 10 ng/ml for the measurement of lansoprazole in 500 μl of human serum.

**Population Pharmacokinetic Analysis**

Population pharmacokinetic analysis was carried out using the NONMEM program (version V, level 1.1)19 running on a ThinkCentre A50p (8195-CTJ) computer (IBM). We used the first-order conditional estimation method and NONMEM-PREDPP library subroutines ADVAN3 and TRANS4 for the 2-compartment model with intravenous dosing. The volume of the central compartment in the i-th individual (Vci) was modeled using the following equation:

\[ V_{ci} = \theta_i \cdot WT \cdot \exp(\eta_{Vci}) \]  

where \( \theta_i \) is the predicted population mean volume of the central compartment and \( \eta_{Vci} \) is a random variable with a mean of zero and variance of \( \omega_{Vci}^2 \). The clearance in the i-th individual (CLi) was modeled using the following equation:

\[ CL_i = \frac{\theta_i}{\theta_j} \cdot \theta_{\text{WT}} \cdot WT \cdot \exp(\eta_{CLi}) \]  

where \( \theta_i \) is the predicted population mean systemic clearance in the homoEM group, \( \theta_j \) is the heteroEM/homoEM clearance ratio, \( \theta_{\text{WT}} \) is the PM/homoEM clearance ratio. That is, both \( \theta_i \) and \( \theta_j \) are fixed to one for a subject with CYP2C19*1/*1, \( \theta_{\text{WT}} \) is fixed to one for a subject with CYP2C19*1/*2 and *1/*3 alleles, and \( \theta_j \) is fixed to one for a subject with CYP2C19*2/*2, *2/*3, and *3/*3. \( \eta_{CLi} \) is a random variable with a mean value of zero and variance of \( \omega_{CLi}^2 \). In addition, the volume of the peripheral compartment in the i-th individual (Vpi) was modeled using the following equation:

\[ V_{pi} = \theta_i \cdot WT \cdot \exp(\eta_{Vpi}) \]  

where \( \theta_i \) is the predicted population mean volume of the peripheral compartment and \( \eta_{Vpi} \) is a random variable with a mean of zero and variance of \( \omega_{Vpi}^2 \). Intercompartmental clearance in the i-th individual (Qi) was modeled using the following equation:

\[ Q_i = \theta_k \cdot WT \]  

where \( \theta_k \) is the predicted population mean value for intercompartmental clearance. Finally, the serum lansoprazole concentration was modeled using the following equation:

\[ C_{\text{pred},j} = C_{\text{pred},j} \cdot (1 + \varepsilon_{CV}) + \varepsilon_{ADD} \]  

where \( C_{\text{pred},j} \) is the j-th observed serum concentration in the i-th subject, \( C_{\text{pred},j} \) is the j-th predicted serum concentration in the i-th subject, and \( \varepsilon_{CV} \) and \( \varepsilon_{ADD} \) are residual intraindividual variations with a mean value of zero and variances of \( \sigma_{CV}^2 \) and \( \sigma_{ADD}^2 \). The magnitude of the variation of \( \varepsilon_{CV} \) can be viewed as the ‘proportional’ component of the residual error model, while that of \( \varepsilon_{ADD} \) can be seen as the ‘additive’ component. NONMEM provides estimates of the standard error.
(S.E.) for all parameters, and S.E. data can be used to define 95% confidence intervals (CI) for true parameter values as follows: 95% CI=(estimated parameter value)±1.96·S.E.106

RESULTS AND DISCUSSION

The main objective of the present study was to estimate the population pharmacokinetic parameters of intravenously administered lansoprazole, and also to evaluate the effect of CYP2C19 polymorphisms on the pharmacokinetics of the drug. The pharmacokinetic data were obtained from a total of 56 subjects (8 PMs, 32 heteroEMs, and 16 homoEMs). The population pharmacokinetic analysis was performed using NONMEM software, because the NONMEM analysis enables us to simultaneously evaluate the mean pharmacokinetic parameters, the covariates affecting the pharmacokinetics of a drug, and also the intra- and interindividual variability of the pharmacokinetics. In addition, the effect of CYP2C19 polymorphisms on proton pump inhibition by lansoprazole was evaluated with 24-h intragastric pH monitoring. The pharmacodynamic data were obtained from 32 (8 PMs, 15 heteroEMs, and 9 homoEMs) of 56 subjects.

Figure 1 shows the observed serum concentrations of lansoprazole following intravenous administration. Marked interindividual variability was observed in the serum concentration profiles following intravenous infusion of 30 mg lansoprazole over 30 min (Fig. 1A). Higher lansoprazole levels were observed in the heteroEM group when compared to the homoEM group. In addition, the serum lansoprazole levels in the PM group were considerably higher than those in the heteroEM group. The elimination half-life of lansoprazole following single intravenous administration was significantly shorter in the homoEM and heteroEM groups than in the PM group (Fig. 1A). Concentration–time curves for lansoprazole following repetitive twice-daily infusions at 5 d were similar to those on day 1 (Figs. 1A, B). The distribution and elimination half-life of lansoprazole after bolus injection at a dose of 30 mg was similar to that after the 30-min infusion, and serum drug concentrations in the heteroEM group were also higher than those in the homoEM group (Figs. 1A, C). In addition, the serum concentrations of lansoprazole after a single infusion of 15 mg were approximately 50% lower than those after 30 mg infusion (Figs. 1A, D). These findings indicate that the pharmacokinetics of lansoprazole administered intravenously was constant and linear in the tested dose range.

One thousand and sixty-nine of serum lansoprazole concentration data points from a total of 56 subjects were analyzed using a 2-compartment pharmacokinetic model. The population pharmacokinetic parameters are summarized in Table 1. The mean value of $V_1$ ($\theta_q$) was estimated to be 0.110 l/kg, and the mean value of $CL$ in the homoEM group ($\theta_q$) was estimated to be 0.179 l/h/kg. The mean value of $CL$ in the heteroEM group was estimated to be 0.129 l/h/kg, and in the PM group was estimated to be only 0.149 l/h/kg. These mean clearance values coincided very well with those calculated from the population pharmacokinetic parameters in Table 1 (0.179, 0.179·0.612, and 0.179·0.212 l/h/kg). The gene-dose effect of CYP2C19 polymorphisms on the clearance of lansoprazole seemed to be comparable with that of intravenously infused omeprazole.15 Specifically, Uno et al. reported that the mean clearance values of omeprazole given intravenously at the dose of 20 mg were 14.6, 8.9, and 3.0 l/h in homoEMs, heteroEMs, and PMs, respectively.15

In the present study, 16 subjects (8 PMs, 7 heteroEMs, and 1 homoEM) received twice-daily drip infusions of 75 mg roxatidine acetate repetitively for 5 d, and 24-h intragastric pH monitoring was performed on day 1 and day 5. Figure 5A shows the mean 24-h intragastric pH profiles before and after...
administration of roxatidine acetate. The mean intragastric pH in the 16 subjects before administration of roxatidine acetate was approximately 2, and the pH value was transiently increased by food intake. Because roxatidine acetate is predominantly eliminated by renal excretion,20) H2-receptor blockade by the drug was not influenced by the CYP2C19 polymorphisms in the present study. The intragastric pH on day 1 was increased by treatment with 75 mg roxatidine acetate (Fig. 5A). The percentage of time with intragastric pH less than 4 is highly correlated with severity of mucosal in-

<table>
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<th>1-Compartment</th>
<th>Estimate</th>
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<td>(q_5) (l/kg)</td>
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<td>(q_6) (l/h/kg)</td>
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<td>(ADD) (ng/ml)</td>
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jury, and drug therapy that raises intragastric and/or intraeosophageal pH above 4 achieves the best clinical results.\textsuperscript{21,22}) The inhibitory effect of roxatidine acetate on gastric acid secretion, therefore, was evaluated as the percentage of time with intragastric pH above 4. The mean (±S.D.) percent of time with a pH above 4 was 43.9±18.7% and 30.3±15.8% in the daytime (9:00–21:00) and nighttime (21:00–9:00), respectively. On the other hand, the intragastric pH on day 5 was lower than that on day 1 (Fig. 5A), suggesting that partial tolerance to the antisecretory effect of roxatidine acetate developed following repetitive administration of the drug. This attenuation of antisecretory activity has also been documented for other H\textsubscript{2}-receptor antagonists.\textsuperscript{3,23}) Netzer et al. reported that tolerance to the antisecretory activity of ranitidine develops during infusion for 72-h periods leading to a loss of pH control.\textsuperscript{3} In addition, Komazawa et al. reported that tolerance occurs during 14 d of continuous famotidine administration.\textsuperscript{23})

In the present study, 16 subjects (8 PMs, 7 heteroEMs, and 1 homoEM) also received 30 mg lansoprazole repetitively for 5 d, and 24-h intragastric pH monitoring was performed on day 1 and day 5. In additional 16 subjects (8 heteroEMs, and 8 homoEM), 30 mg lansoprazole was infused two times at a 12-h interval, and 24-h intragastric pH monitoring was performed on day 1. Figure 5B shows the mean 24-h intragastric pH profile before and after administration of 30 mg lansoprazole to 8 PMs. The mean value of intragastric pH on day 1 was approximately 6, and the mean (±S.D.) percent of time with pH above 4 was 84.3±5.5% and 95.9±6.1% in the daytime and nighttime, respectively (Fig. 5B). Figure 5C shows the mean 24-h intragastric pH profiles before and after administration of 30 mg lansoprazole to 15 heteroEMs. The mean value of intragastric pH on day 1 was approximately 5, and the mean (±S.D.) percent of time with pH above 4 was 70.7±16.2% and 79.2±14.0% in the daytime and nighttime, respectively (Fig. 5C). Figure 5D shows the mean 24-h intragastric pH profile before and after administration of 30 mg lansoprazole to 9 homoEMs. The mean value of intragastric pH on day 1 was approximately 4, and the mean (±S.D.) percent of time with pH above 4 was 43.9±30.7% and 53.5±30.4% in the daytime and nighttime, respectively (Fig. 5D). These results indicate that twice-daily infusion of a 30 mg dose leads to significant proton pump inhibition even in homoEMs despite the short elimination half-life of the drug (Fig. 1). The present findings for lansoprazole were comparable to earlier findings for omeprazole.\textsuperscript{24}) Sugimoto et al. previously reported that the median intragastric pH for the first 24 h following twice daily intravenous administration of 20 mg omeprazole was 6.1, 5.8 and 3.9 in PM, heteroEM, and homoEM groups, respectively.\textsuperscript{24} In addition, no significant tolerance to the antisecretory effect of lansoprazole was observed in the present study. Although the number of subjects who received twice-daily infusions of 30 mg lansoprazole for 5 d was only 8, 7, and 1 in the PM (Fig. 5B), heteroEM (Fig. 5C), and homoEM (Fig. 5D) groups, respectively, the mean intragastric pH in these subjects on day 5 was still higher than that on day 1.

In conclusion, we estimated the population pharmacokinetic parameters of lansoprazole using NONMEM software and evaluated proton pump inhibition in healthy male Japanese subjects. The present study indicates that CYP2C19*2
and *3 alleles are responsible for the pharmacokinetic variability of intravenously administered lansoprazole among Japanese. These findings may provide information for the proper use of lansoprazole injections to treat patients with upper gastrointestinal bleeding.

REFERENCES


