**Note**

*Effect of Water Intake on Pharmacokinetics of Lansoprazole from Fast Disintegrating Tablet in Human Subjects*

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**Summary:** Lansoprazole fast disintegrating tablet (LFDT) has been developed as a multiple unit formulation to increase the QOL of patients, i.e., easy intake without water. However, there is a possibility that patients intake LFDT in accordance with clarithromycin and amoxicillin with water. To study the effect of water on the absorption of lansoprazole (LPZ), the study was carried out using human volunteers. After selected by phenotype of LPZ metabolism, extensive metabolizers (EMs) of LPZ were used in this study. Twelve healthy male EMs took LFDT containing 30 mg LPZ with 150 mL of water and without-water, i.e., with saliva, to study the pharmacokinetics of LPZ from the gastrointestinal tract by a cross-over manner with one-week washout period under fasted condition in the morning. The mean AUC₀₋₂₄ were 2004.4 ± 973.6 ng·h/mL in without-water experiment and 2018.5 ± 1159.6 ng·h/mL in the case of with-water experiment. Mean Cmax were 851.9 ± 450.8 ng/mL in without-water experiment and 830.8 ± 456.8 ng/mL in with-water experiment, respectively. ANOVA was applied to the log-transformed AUC₀₋₂₄ and Cmax values. The 90% two sided confidence intervals for log-transformed AUC₀₋₂₄ was 0.78–1.22 and that for log-transformed Cmax was 0.67–1.37, respectively. By comparing these pharmacokinetic parameters, we may state that there was no significant difference between the two administration modes.

**Key words:** lansoprazole; phenotype; genotype; human subjects; pharmacokinetics

**Introduction**

To increase the compliance and QOL of the patients having gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome etc., lansoprazole (LPZ) is used clinically. LPZ is a strong proton pump inhibitor having inhibitory activity on gastric ulcer formation and accelerates the ulcer healing by inhibiting the acid production in the parietal cells through the inhibition of H⁺-K⁺-ATPase. As LPZ is unstable in the stomach, i.e. gastric acid, enteric coated granules are filled in a capsule. LPZ is widely used for the Helicobacter pylori eradication therapy in combination with clarithromycin and amoxicillin. Clinically, LPZ is prescribed to elderly patients whose swallow function is reduced with high frequency. In the case of LPZ capsule, patients must intake capsule with water. To improve the compliance and QOL of those elderly patients, LPZ fast disintegrating tablets (LFDT) has been developed, where LPZ is compressed with pharmaceutical additives such as binder and disintegrator etc. and supplied as tablet. Our previous report showed that LFDTs, 15 mg and 30 mg, were bioequivalent to conventional LPZ capsules containing 15 mg and 30 mg LPZ. In addition, LFDT was shown to dissolve within 30 seconds. The diameter of LFDT is 12.1 mm for 30 mg tablet and 9.1 mm for 15 mg tablet. In the mouth, LFDT immediately disintegrates and releases LPZ granules and are rapidly swallowable. From these results, we can state that the elderly patients...
who lack swallow function will take LFDT with ease. However, as LFDT disintegrates within 30 seconds in the oral cavity, we cannot deny the possibility that LPZ is absorbed from the oral cavity and shows a different pharmacokinetic profile from that of the conventional preparation containing LPZ. In this case, a possibility that LFDT is administered with water together with other drugs arises. In the present study, the effect of water intake on the serum LPZ concentration vs. time profile has been studied by a pharmacokinetic analysis.

LPZ is known to have a large inter-subject variability of clearance due to polymorphism. In such cases, the guideline for the bioequivalence studies recommends to select the larger clearance subject group of the drug in the clinical study.14 In this study, the larger clearance subjects of the drug, Extensive Metabolizer (EM) were focused.

Materials and Methods

Materials: LPZ fast disintegrating tablets (LFDT) and LPZ capsules containing 30 mg LPZ were obtained from Takeda Chemical Industries, Ltd (Osaka, Japan). LPZ: [(±)-2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyrirdyl]methyl]sulfinyl]-benzimidazole, LPZ sulphone: [2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyrirdyl]methyl]sulfonyl]-benzimidazole] and hydroxy LPZ: [(±)-5-hydroxy-2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyrirdyl]methyl] sulfinyl]-benzimidazole were also obtained from Takeda Chemical Industries. β-glucuronidase was purchased from Sigma (St. Louis, MO, USA). Dichloroethane, acetonitrile and ethanol were of HPLC grade. All other reagents were of analytical-reagent grade.

Methods: Human subjects: Twelve healthy human subjects aged between 20 – 24 years were enrolled in this study. Their body weights were 50.1 – 72.6 kg and body-mass index (BMI) were 18.2 – 22.3. They were given informed consent after fully explaining about the study protocol. Informed consent was approved by the IRB of the Kyushu Clinical Pharmacology Research Clinic (Fukuoka, Japan). No other drug or alcoholic beverage was allowed prior to or during the study period. They received 30 mg LPZ capsule in order to determine the phenotype of LPZ. At 4 h after oral administration, 5 mL of blood sample was obtained from the cubital arm vein of each subject. After centrifuging at 3,000 g for 20 min, serum sample was obtained and LPZ sulphone, a metabolite of LPZ, concentration was measured by HPLC method. According to the method of Nakamura et al., all subjects were confirmed to be extensive metabolizers (EMs) from their serum LPZ sulphone levels at 4 h after administration being lower than 100 ng/mL.17 Furthermore, they received the genotyping test. Five mL of blood samples were obtained from their cubital arm veins and white blood cell fractions were separated. The samples were analyzed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method to detect the CYP2C19 genotype at SRL (Tokyo, Japan) according to the reported method.10,11 It has been reported that there are two point mutations in the CYP2C19 gene. The wild-type allele (∗1) has G at position 636 in exon 4 and G at position 681 in exon 5 of CYP2C19. One (∗2 allele) of the mutated alleles has A at position 681 in exon 5. Another mutated allele (∗3 allele) has A at position 636 in exon 4.10

Pharmacokinetic study: Subjects received LFDT, 30 mg, at 9 AM. No food or beverages were allowed for at least 4 h following drug administration. All subjects received the same standardized meals. Grapefruit-containing products and caffeine-containing products were not allowed during the study periods, because these products contain compounds that may affect cytochrome P450-metabolizing enzymes by inhibition or induction. Before administration, blank blood sample, 5 mL, was obtained. Thereafter, they received one LFDT in the morning in the fasted condition with or without water in a cross-over manner with a one-week washout period. The volume of water adopted was 150 mL as a glass of water, which was suggested by Welling et al. and Koch et al.15,20 After administration, blood samples were obtained at 30 min and thereafter at 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Serum samples were obtained after centrifugation and were frozen at −20°C until analysis.

Analysis of LPZ and its main metabolites in the serum samples: The serum concentrations of LPZ and its main metabolites, LPZ sulphone and hydroxy LPZ, were determined by a HPLC method.21 LPZ was extracted from 0.5 mL of the serum sample by liquid-liquid extraction method with 3 mL of diethyl ether-dichloromethane mixture (7:3, v/v). The extract was evaporated to dryness under a stream of nitrogen gas and was reconstituted with 200 μL of acetoniitrile-water (7:3, v/v) of which 100 μL was injected to the HPLC system. The analytical column was a TSK gel ODS-120T (4.6 × 150 mm, Tosoh, Tokyo, Japan) and the mobile phase was water-acetonitrile-n-octylamine (620:380:1, v/v), adjusted to pH 7.0 with 85% phosphoric acid. The flow rate was 1.0 mL/min. LPZ and LPZ sulfone were detected at 285 nm and hydroxy LPZ at 303 nm. Levels were estimated by the chromatographic technique of comparing peak areas obtained from LPZ, metabolites and internal standard (IS). Isobutyl-p-hydroxybenzoate was used as an IS. A set of five calibration standards was run with each series of the samples. The inter-day variations were less than 5.0%. Linear calibration curves were obtained between 5 ng/mL and 2000 ng/mL and the correlation coefficients were greater than 0.99. The limit of quantification was 10 ng/mL for
LPZ, LPZ sulphone and hydroxyl LPZ, respectively.\textsuperscript{22} As hydroxyl LPZ partly exists as glucuronides, total LPZ capsule concentration was determined after hydrolysis with \(\beta\)-glucuronidase.

Pharmacokinetic analysis: A non-compartmental pharmacokinetic analysis was applied to the data. The terminal elimination rate constant (\(k_d\)) was determined by a linear regression of at least three data points from the terminal portion of the logaritmic serum drug or metabolite concentration-time plots. The area under the serum concentration-time curve from time zero to 24 h (AUC\textsubscript{0-24}) was calculated using the linear trapezoidal method. The AUC\textsubscript{0-\(\infty\)} from time zero to infinity was calculated by adding the correction term, AUC\textsubscript{0-\(\infty\)} to AUC\textsubscript{0-24}, where AUC\textsubscript{0-\(\infty\)} was determined by addition of the correction term, \(\text{Cp(24h)/}k_d\). The area under the first moment curve from time zero to 24 h (AUMC\textsubscript{0-24}) was also calculated with the linear trapezoidal method. The AUMC\textsubscript{0-\(\infty\)} was calculated by addition of the correction term, AUMC\textsubscript{0-\(\infty\)} to AUMC\textsubscript{0-24}, where AUMC\textsubscript{0-\(\infty\)} was determined by addition of the correction term, \(\text{Cp(24h)/}k_d + \text{Cp(24h)/}k_d^2\). The terminal elimination half-life, \(t_{1/2}\), was determined by dividing \(\ln 2\) by \(k_d\). The mean residence time (MRT) was determined by AUMC\textsubscript{0-\(\infty\)}/AUC\textsubscript{0-\(\infty\)}.

Statistics: Pharmacokinetic parameters for LPZ were evaluated using an analysis of variance (ANOVA) with fixed effect for “sequence or carry-over”, “period” and “subjects nested within sequence”. Within framework of ANOVA for common logarithms of AUC\textsubscript{0-\(\infty\)} and \(C_{\text{max}}\), 90% two sided confidence intervals for the ratio of least squares means of with-water to without-water were provided. The 90% two sided confidence intervals were obtained by taking the anti-log of the 90% two sided confidence interval for the difference between the least squares means on the common logarithmic scale. When the ratios of the mean AUC\textsubscript{0-24} and \(C_{\text{max}}\) of with-water to without-water were within the range of 0.8–1.25, the two conditions were proved to be bioequivalent according to the Guidelines for Bioequivalence Studies of Generic Products (Equivalence Study Guidelines), National Institute of Health Sciences Japan.\textsuperscript{4} All the parameter values are expressed with their mean ± SD.

Results and Discussion

All volunteers were judged as the EMs by phenotyping, based on their serum LPZ sulphone levels at 4 h after oral administration of 30 mg LPZ capsule. It was reported that phenotype and genotype did not always agree.\textsuperscript{22} To ascertain the genotype of the subjects, the genotyping test for their CYP2C19 gene was performed in this study. From the results of genotyping test for their CYP2C19 gene, 4 volunteers had CYP2C19*1/*1 and 8 volunteers had CYP2C19*1/*2. Of the nominat-
Table 1. 6 Pharmacokinetic parameters of Lansoprazole and the results of ANOVA between the two administration modes

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pharmacokinetic parameters</th>
<th>Administration mode</th>
<th>Difference between two administration modes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without water*</td>
<td>With water**</td>
</tr>
<tr>
<td>30 mg</td>
<td>AUC0-24 (ng·hr/mL)</td>
<td>2004.4 ± 973.6</td>
<td>2018.5 ± 1159.6</td>
</tr>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>851.9 ± 450.8</td>
<td>830.8 ± 456.8</td>
</tr>
</tbody>
</table>

*: 30 mg LFDT was administered without water.
**: 30 mg LFDT was administered with 150 mL water.
***: The values indicate the log-transformed AUC0-24 or Cmax.

Fig. 2. Serum Lansoprazole and its metabolites concentrations vs. time curves after oral administrations of 30 mg LFDT with 150 mL of water, ● Lansoprazole (LPZ), ○ LPZ sulphone, □ hydroxy LPZ and ◊ LPZ sulphone glucuronide. Each point shows the mean ± SD (LPZ) or the mean (its metabolites) of 12 subjects.

ed 12 healthy male volunteers, 4 subjects (33.3%) were homo-EMs and 8 subjects (66.7%) were hetero-EMs. The incidence of homo- and hetero-EMs in this study agreed with previous reports. Fig. 1 shows the mean serum LPZ concentrations vs. time curves following administration of 30 mg LFDT with saliva. After administration, plasma LPZ concentration increased and reached its maximum level, Cmax, at about 1 h. Non-compartmental pharmacokinetic analysis was applied to these data and the calculated pharmacokinetic parameter values are shown in Table 1. The mean AUC0-24 and the mean Cmax were 2004.4 ± 973.6 ng·h/mL and 851.9 ± 450.8 ng/mL, respectively. Fig. 2 shows the mean serum LPZ concentrations vs. time curves following administration of 30 mg LFDT with 150 mL of water. The mean AUC0-24 and Cmax of LPZ were 2018.5 ± 1159.6 ng·h/mL and 830.8 ± 456.8 ng/mL, respectively. These values clearly indicate that there is no significant difference on serum LPZ concentration vs. time curve between the two groups. As observed in Figs. 1 and 2, the serum LPZ metabolites concentrations vs. time curves also did not show any difference between the two modes of administration. To test the bioequivalence between the two modes of administration, ANOVA was applied to the log-transformed AUC0-24 and Cmax values. The 90% two sided confidence intervals for log-transformed AUC0-24 was 0.78-1.22 and that for log-transformed Cmax was 0.67-1.37, respectively. By comparing these pharmacokinetic parameters, we may state that there was no significant difference between the two modes of administration. LFDT is clinically used in combination with other
drugs, for example, in Helicobacter pylori eradication therapy. In these cases, patients take LFDT together with water, because LFDT is prescribed with other drugs, clarithromycin, and amoxicillin etc. In biopharmaceutics, “solvent drag” phenomenon is a well-known concept, i.e., the absorption of drugs that are absorbed from the small intestine by passive diffusion, for example terbutaline, is affected by convective transmucosal fluid flow. Taking these points into consideration, there is a possibility that intake of LFDT with water shows a higher serum LPZ concentration vs. time curves than without-water intake. To clarify whether there is any difference on the pharmacokinetic parameters between with-water group and without-water group, pharmacokinetic study was performed. However, no difference in the serum LPZ concentrations vs. time curves between the two modes of administration was observed. In addition, there was no significant difference on the pharmacokinetic parameters between the two groups, i.e., without and with-water groups. Solvent drag phenomenon was observed in the in vitro perfusion experiment using rat small intestine, where much water was used as compared to the volume of the intestinal luminal space. However, in this study, the volume of water used for the administration of LFDT was 150 mL. Furthermore, the water was not directly infused into the small intestine. Therefore, the effect of water intake on the absorption of LPZ from LFDT was not observed in this study. These results support the usefulness of LFDT in the combination therapy with antibiotics against Helicobacter pylori infectious disease, i.e., gastric ulcer.

In conclusion, a novel fast disintegrating tablet LPZ, 30 mg, shows the same serum LPZ concentration vs. time curves as the conventional LPZ capsule, 30 mg. The mean Cmax and AUC0-24 are almost the same values, i.e., 851.9 ± 450.8 ng/mL and 2004.4 ± 973.6 ng·h/mL (without water), and 830.8 ± 456.8 ng/mL and 2085.5 ± 1159.6 ng·h/mL (with water), respectively. After the oral administration of LFDT, it disintegrates fast in the subject mouths. Swallowing of LFDT without-water or administration of LFDT with water has the same bioavailability. LFDT can be safely used instead of the conventional LPZ capsule.

References


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