Evaluation of Fast Disintegrating Lansoprazole Tablet in Human Subjects

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Summary: Fast disintegrating lansoprazole tablet (LFDT) has been developed as a multiple unit formulation and evaluated using human subjects as compared to the conventional lansoprazole (LPZ) capsule containing enteric coated granules. Twelve healthy male volunteers, who were confirmed as extensive metabolizers (EMs) based on the plasma levels of LPZ sulphone metabolite, were enrolled into the study and genotype of CYP2C19 was confirmed. They kept 30 mg LFDT in their mouths for 2 min and the saliva was recovered without swallow. Eight subjects did not show LPZ in their serum after intake. Although LPZ was detected in 4 subjects’ serum, their concentrations were less than 5 ng/mL. LPZ was thought to be not absorbed from the oral cavity. LFDT was orally administered to 12 healthy male EMs at two doses, 15 mg and 30 mg, and serum LPZ concentrations were measured. The mean Cmax and AUC0–24 were 474.1 ± 254.0 ng/mL and 1105.3 ± 1101.4 ng·h/mL (15 mg) and 992.8 ± 384.3 ng/mL and 2216.5 ± 1270.1 ng·h/mL (30 mg). By comparing to that obtained after oral administration of the same doses of LPZ capsule, serum LPZ concentration vs. time curve was almost the same level, i.e., Cmax and AUC0–24 did not have significant differences. From these results, LFDT has been shown to be equivalent to LPZ capsule and will show the same acid suppressing effects in the clinical situation.

Key words: lansoprazole; phenotype; genotype; extensive metabolizer (EM); human subjects; pharmacokinetics

Introduction

LPZ is a strong proton pump inhibitor (PPI) having an 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.1-3 As LPZ is unstable against acid, magnesium carbonate is formulated in a LPZ capsule as a pharmaceutical additive to increase the stability of LPZ. In addition, LPZ is filled in a capsule as enteric granules of which mean diameter is 1.1 mm as shown in Fig. 1a. These enteric granules are filled in a #1 gelatin capsule for 30 mg and in a #3 gelatin capsule for 15 mg preparations.4,5 LPZ capsule is widely used in the world for the therapy of gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome etc.6 Clinically, LPZ is prescribed to elderly patients whose swallow function is reduced with high frequency.7 Therefore, a new LPZ preparation that is useful for swallow-function-deficient patients is needed. By introducing a fast disintegrating tablet technology that makes tablet swallowable without water as an easily-in-take pharmaceutical preparation, LPZ fast disintegrating tablets (LFDT) has been developed. As shown in Fig. 1b, LFDT contains enteric LPZ granules having smaller particle size (mean diameter of 350 μm) than those used in LPZ capsule. The in vitro dissolution study using pH 6.8 dissolution medium showed that both LFDT and LPZ capsule had the same dissolution characteristics.8-10 In addition, LFDT was shown to dissolve within 30 seconds.8-10 The diameter of LFDT is 12.1 mm for 30 mg tablet and 9.1 mm for 15 mg tablet.

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In the mouth, LFDT immediately disintegrates and releases LPZ granules and are rapidly swallowable. From these results, we can state that the elder 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 the conventional preparation of LPZ. Therefore, an evaluation study has been performed to clarify whether LPZ is absorbed from the oral cavity and shows the same pharmacokinetic characteristic after oral intake in comparison with the conventional LPZ preparation.

**Material and Methods**

**Preparations and reagents:** LPZ fast disintegrating tablets (LFDT) and LPZ capsules containing 15 mg or 30 mg LPZ were obtained from Takeda Chemical Industries, Ltd (Osaka, Japan). LPZ: [(±)-2-[[3]-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole, LPZ sulphone: [2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]-benzimidazole and hydroxy LPZ: [(±)-5-hydroxy-2-[[3]-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]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.

**Human subjects:** Healthy 12 human subjects were enrolled in this study. Their ages were 20–24 years. 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 explained 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., extensive metabolizers (EMs) were confirmed from their serum LPZ sulphone levels at 4 h after administration being lower than 100 ng/mL. After identifying the phenotype, they received the genotyping test. Namely, 5 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 method of previous report. 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 689 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 4.14)

**Pharmacokinetic study:** Subjects received test LPZ preparation at 09 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. 24 subjects received both preparations, LFDT and LPZ capsule at two dose levels, 15 mg and 30 mg. Before administration, blank blood sample, 5 mL, was obtained. Thereafter, they received either one LFDT or LPZ capsule in the morning in the fasted condition with 150 mL water or without water by a cross-over manner with a one-week washout period. 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.

To study the absorption of LPZ from the oral cavity, 12 subjects kept 30 mg LFDT in their mouth for 2 min and the contents in the oral cavity were recovered without swallowing (Recovery dosing). In another day after one-week washout period, the same subjects swallowed the same LFDT with 150 mL water (Swallowing dosing). Before drug administration, 5 mL of blank blood was obtained from their cubital arm vein. After drug administration, blood samples were obtained at 10, 20 and 30 min and thereafter at 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h in both cases, and the obtained serum samples were also frozen at −20°C until analysis.

**Analysis of LPZ in the salivary samples:** The concentrations of LPZ in the salivary samples recovered from the human volunteer’s oral cavity were also determined by a HPLC method. To 150 μL of the salivary sample, 15 mL of 1 mol/L sodium hydroxide solution, 110 mL of acetonitrile and 2.75 mL of triethylamine were added, and the mixture was adjusted to pH 10.0 with 85% phosphoric acid. After centrifugation at 13,000 rpm for 10 min, 10 mL of the supernatant was injected to HPLC system. The analytical column was a Capcell pak C18 SG120 (Shiseido, Tokyo, Japan) and the mobile phase was water-acetonitrile-triethylamine (60:40:1, v/v) adjusted to pH 7.0 with 85% phosphoric acid. The flow rate was 1.0 mL/min. LPZ were detected at 285 nm. 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 and the correlation coefficients were greater than 0.99. The limit of quantification and the limit of detection were 10 ng/mL and 5 ng/mL for LPZ and the metabolites.10)

**Pharmacokinetic analysis:** A non-compartmental pharmacokinetic analysis was applied to the data. The terminal elimination rate constant (kel) was determined by a linear regression of at least three data points from the terminal portion of the logarithmic serum drug or metabolite concentration-time plots. The area under the serum concentration-time curve from time zero to 24 h (AUC_{0–24}) was calculated using the linear trapezoidal method. The AUC_{0–∞} from time zero to infinity was calculated by adding the correction term, AUC_{0–24}, to AUC_{24–∞}, where AUC_{24–∞} was determined by addition of the correction term, Cp(24 h)/kel. The area under the first moment curve from time zero to 24 h (AUMC_{0–24}) was also calculated with the linear trapezoidal method. The AUMC_{0–∞} was calculated by adding the correction term, AUMC_{24–∞}, to AUMC_{0–24}, where AUMC_{24–∞} was determined by addition of the correction term, 24 h·Cp(24 h)/kel^2. The terminal elimination half-life, t_{1/2}, was determined by dividing ln2 by kel. The mean residence time (MRT) was determined by AUMC_{0–∞}/AUC_{0–∞}.

**Statistics:** Pharmacokinetics parameters for LPZ were evaluated using an analysis of variance (ANOVA) with fixed effect for “sequence or carry-over”, “formu-
Fig. 2. Serum lansoprazole and its metabolites concentrations vs. time curves after oral administrations of (a) 15 mg LFDT and (b) 30 mg LFDT, $\bullet$; lansoprazole (LPZ), $\circ$; LPZ sulphone, $\triangle$; hydroxy LPZ and $\bigodot$; LPZ sulphone glucuronide. Each point shows the mean ± SD (LPZ) or the mean (its metabolites) of 12 subjects.

Pharmacokinetic evaluation of LFDT: Out of 12 healthy subjects, all volunteers were judged as the Ems based on the serum LPZ sulphone level at 4 h after oral administration. From the results of genotyping test for their CYP2C19 gene, 4 volunteers had CYP2C19*1/W and 8 volunteers had CYP2C19*1/W. **Figure 2** shows the serum LPZ concentrations vs. time curves following oral administration of LFDT at two dose levels, 15 mg...
shown in Table 1 the calculated pharmacokinetic parameter values are obtained, though the serum LPZ level were higher than LPZ dose was increased to 30 mg, the same pattern was formed AUC0–24 was within the range of 0.91–1.06 and log-transformed Cmax values and the confidence interval of the difference was within the range of 0.87–1.22 for log-transformed AUC0–24 and 0.89–1.07 for log-transformed AUC0–24 and Cmax respectively. With 30 mg LFDT and LPZ capsule formulations, log-transformed AUC0–24 was within the range of 0.91–1.06 and log-transformed Cmax was within the range of 0.90–1.20, respectively. In both doses, i.e. 15 mg and 30 mg, the differences of log-transformed AUC0–24 and Cmax were within the range of 0.8–1.25. Therefore, we may state that LFDT and LPZ capsule are bioequivalent.

Absorption of LPZ from oral cavity: To study the possibility of the absorption of LPZ from the oral cavity, both LPZ and its metabolites were measured in the subject’s serum after swallowing dosing and recovery dosing of 30 mg LFDT. Fig. 4a and 4b show the results. In the case of recovery dosing study, saliva samples were obtained at 2 min after the intake of LFDT and the salivary LPZ levels were measured. Also serum LPZ concentration was measured and Fig. 4b shows the results. In the case of swallowing dosing, LPZ was detected in the serum of all the subjects for 24 h as

(Fig. 2a) and 30 mg (Fig. 2b). After oral administration of 15 mg LFDT, it dissolved fast in their mouths and was swallowed into the stomach. Serum LPZ level increased thereafter and reached to its maximum level, Cmax, at about 2 h. The mean Cmax and Tmax were 474.1 ± 254.0 ng/mL and 1.75 ± 1.11 h, respectively. When the LPZ dose was increased to 30 mg, the same pattern was obtained, though the serum LPZ level were higher than that of 15 mg preparation and was well correlated with the administered dose of LPZ. Non-compartmental pharmacokinetic analysis was applied to those data and the calculated pharmacokinetic parameter values are shown in Table 1. The mean Cmax, AUC and Tmax at 30 mg LPZ preparation were 992.8 ± 384.3 ng/mL and 2216.5 ± 1203.0 ng·h/mL, 1.91 ± 0.88 h, respectively. When the swallowing dosing, LPZ was swallowed into the stomach. Serum LPZ level of 15 mg LFDT, it dissolved fast in their mouths and was well correlated with the administered dose of LPZ preparation, capsule, the same study was performed and the result is shown in Fig. 2a and 2b. By comparing Figs. 2 and 3, we may state that there is not a significant difference on serum LPZ and its metabolites concentrations vs. time curves between the two preparations, LFDT and LPZ capsule. To test the bioequivalence of the two preparations, ANOVA was applied to the log-transformed AUC0–24 and Cmax values and the result is shown in Table 1. With the two formulations, i.e. 15 mg LFDT and LPZ capsule, 90% two-sided confidence interval of the difference was within the range of 0.89–1.07 for log-transformed AUC0–24 and 0.87–1.22 for log-transformed Cmax, respectively. With 30 mg LFDT and LPZ capsule formulations, log-transformed AUC0–24 was within the range of 0.91–1.06 and log-transformed Cmax was within the range of 0.90–1.20, respectively. In both doses, i.e. 15 mg and 30 mg, the differences of log-transformed AUC0–24 and Cmax were within the range of 0.8–1.25. Therefore, we may state that LFDT and LPZ capsule are bioequivalent.

Absorption of LPZ from oral cavity: To study the possibility of the absorption of LPZ from the oral cavity, both LPZ and its metabolites were measured in the subject’s serum after swallowing dosing and recovery dosing of 30 mg LFDT. Fig. 4a and 4b show the results. In the case of recovery dosing study, saliva samples were obtained at 2 min after the intake of LFDT and the salivary LPZ levels were measured. Also serum LPZ concentration was measured and Fig. 4b shows the results. In the case of swallowing dosing, LPZ was detected in the serum of all the subjects for 24 h as

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pharmacokinetic parameters</th>
<th>Test preparation</th>
<th>Difference between LFDT and LPZ capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg</td>
<td>AUC0–24 (ng·h/mL)</td>
<td>1105.3 ± 1101.4</td>
<td>1136.2 ± 1186.2</td>
</tr>
<tr>
<td></td>
<td>(ng/mL)</td>
<td>1136.2 ± 1186.2</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Tmax (h)</td>
<td>1.75 ± 1.11</td>
<td>1.91 ± 0.85</td>
</tr>
<tr>
<td></td>
<td>MRT* (h)</td>
<td>2.72 ± 0.91</td>
<td>3.04 ± 1.10</td>
</tr>
<tr>
<td></td>
<td>AUC0–24*** (ng·h/mL)</td>
<td>1182.5 ± 1147.1</td>
<td>1147.3 ± 2182.8</td>
</tr>
<tr>
<td></td>
<td>k1i (1/h)</td>
<td>0.65 ± 0.18</td>
<td>0.64 ± 0.17</td>
</tr>
<tr>
<td>30 mg</td>
<td>AUC0–24 (ng·h/mL)</td>
<td>2216.5 ± 1203.0</td>
<td>2232.6 ± 1203.0</td>
</tr>
<tr>
<td></td>
<td>(ng/mL)</td>
<td>992.8 ± 384.3</td>
<td>949.2 ± 361.6</td>
</tr>
<tr>
<td></td>
<td>Tmax (h)</td>
<td>1.91 ± 0.88</td>
<td>1.62 ± 0.67</td>
</tr>
<tr>
<td></td>
<td>MRT** (h)</td>
<td>2.92 ± 0.85</td>
<td>2.83 ± 0.74</td>
</tr>
<tr>
<td></td>
<td>AUC0–24*** (ng·h/mL)</td>
<td>2206.3 ± 1233.7</td>
<td>2209.8 ± 1171.4</td>
</tr>
<tr>
<td></td>
<td>k1i (1/h)</td>
<td>0.66 ± 0.16</td>
<td>0.67 ± 0.15</td>
</tr>
</tbody>
</table>

*: Each value shows the mean ± S.D of 12 subjects.
**: The values indicate the log-transformed AUC0–24 or Cmax.
***: Two cases (A06 and A10) were excluded, because linear terminal elimination phase was not obtained in them.

LFDT: lansoprazole fast disintegrating tablet
Fig. 3. Serum lansoprazole and its metabolites concentrations vs. time curves after oral administrations of (a) 15 mg LPZ capsule and (b) 30 mg LPZ capsule. •: LPZ, ●: LPZ sulphone, ◦: hydroxy LPZ and □: LPZ sulphone glucuronide. Each point shows the mean ±SD (LPZ) or the mean (its metabolites) of 12 subjects.

shown in Fig. 4a. On the other hand, in the case of recovery dosing, serum LPZ concentrations were detected in only 4 subjects and the measured concentrations were very low, i.e., 1–4 ng/mL. In the remaining 8 subjects, neither LPZ nor its metabolites were detected in their serum for 24 h. Table 2 shows the pharmacokinetic parameters of LPZ such as AUC₀–₂₄ and Cₘₐₓ of LPZ. In the case of recovery dosing, the mean AUC₀–₂₄ was 1910.9 ± 546.0 ng·h/mL and the mean Cₘₐₓ was 978.8 ± 401.6 ng/mL, respectively. In the case of swallowing dosing, the mean AUC₀–₂₄ was 8.0 ± 14.6 ng·h/mL and the mean Cₘₐₓ was 6.8 ± 10.5 ng/mL, respectively. These results suggest the non-absorbability of LPZ from the oral cavity. To make clear the non-absorbability of LPZ from the oral cavity, the salivary recovery of LPZ was studied and the salivary recovery percentage was 100.78 ± 2.28%. Concerning the judgment of the absorption of LPZ from the oral cavity, the method proposed by Stalker D. J. et al. was used with minor modification. Namely, the following criteria were used; when both the mean ratios of AUC₀–₂₄ and Cₘₐₓ (recovery dosing/swallowing dosing) are less than 5.0%, LPZ is not absorbed from the oral cavity. The mean ratios were 0.37 (0.62% for AUC₀–₂₄) and 0.65 (1.01% for Cₘₐₓ), respectively. Therefore, these results suggest that LPZ was not absorbed from
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Fig. 4. Serum lansoprazole concentrations vs. time profiles following (a) swallow administration or (b) recovery administration of 30 mg LFDT, $\bullet$: LPZ, $\bigtriangleup$: LPZ sulphone, $\triangle$: hydroxy LPZ, $\circ$: LPZ sulphone glucronide. Each point shows the mean ± SD (LPZ) or the mean (its metabolites) of 12 subjects.

Discussion

There are two methods for selecting EMs, i.e., based on either phenotype or genotype of the subjects. It was reported that phenotype and genotype did not always agree. Therefore, in this study, phenotyping was used. Namely, the subjects whose serum LPZ sulphone concentrations were less than 100 ng/mL at 4 h after oral administration of 30 mg LPZ capsule were designated to be EM. Of the nominated 12 healthy male volunteers, 4 subjects (33.3%) were homo-EMs and 8 subjects (67.7%) were hetero-EMs. The incidence of homo- and hetero- EMs in this study agreed with previous reports.

LFDT is a unique but complicated oral DDS as shown in Fig. 1b. In vitro evaluation study showed that LFDT disintegrated very fast at neutral pH. The pH of the saliva excreted into the oral cavity is normally neutral. LFDT is prepared by compressing enteric granules with pharmaceutical additives such as binder and disintegrator. The enteric granules containing LPZ were designed to dissolve at neutral pH. Therefore, it is plausible that the enteric coating layer dissolves in the mouth when LFDT is kept in the oral cavity for a long time.
Table 2. Pharmacokinetic parameters of lansoprazole (LPZ) and salivary recovery rate of two administration modes

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>AUC₀-２４ (ng・h/mL)</th>
<th>Cₘₐₓ (ng/mL)</th>
<th>Salivary recovery percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(R)*</td>
<td>(S)** (%)</td>
<td>(R)* (%)</td>
</tr>
<tr>
<td>A01</td>
<td>48</td>
<td>2505</td>
<td>1.9</td>
</tr>
<tr>
<td>A02</td>
<td>0</td>
<td>1000</td>
<td>0.0</td>
</tr>
<tr>
<td>A03</td>
<td>0</td>
<td>1412</td>
<td>0.0</td>
</tr>
<tr>
<td>A04</td>
<td>12</td>
<td>1749</td>
<td>0.7</td>
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<tr>
<td>A05</td>
<td>13</td>
<td>2014</td>
<td>0.6</td>
</tr>
<tr>
<td>A06</td>
<td>0</td>
<td>2797</td>
<td>0.0</td>
</tr>
<tr>
<td>B01</td>
<td>0</td>
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<td>B02</td>
<td>0</td>
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<td>0</td>
<td>1413</td>
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</tr>
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<td>B05</td>
<td>0</td>
<td>1295</td>
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</tr>
<tr>
<td>B06</td>
<td>24</td>
<td>1997</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Mean ± SD 8.0 ± 14.6 1910.9 ± 546.0 0.37 ± 0.62 6.8 ± 10.5 978.8 ± 401.6 0.65 ± 1.01 100.78 ± 2.28

* (R): recovery dosing
** (S): swallowing dosing
*** 95% Confidence intervals of the AUC₀-２４ and Cₘₐₓ were calculated by Fieller-method.

However, the disintegration time of LFDT is within 30 seconds,¹⁰ which suggests that LFDT is not swallowable. It is also not conceivable that the enteric granules dissolve in the oral cavity and dissolved LPZ is absorbed from the oral cavity. In this study, the absorption of LPZ from the oral cavity was studied by keeping LFDT in the oral cavity for 2 min without swallowing according to the previously reported method.¹⁶ LPZ was detected in the serum of 4 subjects within 12 subjects. The mean ratio of AUC₀-２４ was 0.37 and the mean ratio of Cₘₐₓ was 0.65. In this study, LFDT was kept in the oral cavity for 2 min and the saliva in the oral cavity was recovered. There is a possibility that the subjects would swallow their saliva accidentally. Therefore, we made a criterion to assess the absorption of LPZ from the oral cavity, i.e., if the ratios of both mean AUC₀-２４ and Cₘₐₓ are less than 5.0, the absorption of LPZ from the oral cavity can be denied. This ratio in the individual subject was in the range of 0.6–0.9 for AUC₀-２４ and 1.4–2.9 for Cₘₐₓ, respectively. Therefore, according to this criterion, LFDT was elucidated to be not absorbed from the oral cavity. Furthermore, almost 100% of the LPZ was recovered from the collected saliva. Hence, LPZ was not absorbed from the oral cavity when LFDT was taken by an ordinary administration method, i.e., swallowing. In addition, LFDT showed almost the same serum LPZ concentration vs. time curves after oral administration to Japanese subjects as conventional LPZ capsule. Because the 90% two-sided confidence interval for log-transformed AUC₀-２４ and Cₘₐₓ was within the range of 0.80–1.25. The carry-over effect was observed in the ANOVA for AUC₀-２４. One possible reason for this result is the different distribution of CYP2C19 genotype between the two groups (sequences). The subjects were, therefore, further classified into homo- and hetero-EMs. By this analysis, approximately 1.5-fold difference was observed for AUC₀-２４. Furthermore, ANOVA was further applied to AUC₀-２４ by taking the genotype of CYP2C19 into consideration. As a result, carry-over effects were not observed. Therefore, the results of the ANOVA of this study are thought to be acceptable.

In the study of 15 mg LPZ formulations, ANOVA was applied to log-transformed AUC₀-２４ and Cₘₐₓ. The carry-over effects were not observed. The two-sided confidence intervals of the formulation difference of log-transformed AUC₀-２４ and Cₘₐₓ were 0.89–1.07 and 0.87–1.22, respectively. ANOVA was also applied to Tmax, MRT, AUC₀-２４, and kₘ. There were no significant differences in any of the parameters except for kₘ. Although there was a significant difference in kₘ between the two formulations, the two-sided 90% confidence interval was within the range of 2.8–8.6%, where the upper and lower limits were within the range of −20% to 20%. The difference was, therefore, considered to be not so large as the mean of kₘ was approximately 0.66 h⁻¹ and the difference of kₘ observed in this study was 0.035 h⁻¹. When ANOVA was applied to both log-transformed AUC₀-２４ and Cₘₐₓ of the subject population, 15 mg LFDT was also shown to be bioequivalent to 15 mg LPZ capsule. In the case of 30 mg study, ANOVA showed no carry-over effects. The two-sided 90% confidence intervals of the difference of log-transformed AUC₀-２４ and Cₘₐₓ were...
and Tmax are 992.8 ± 0.91 h, respectively. Thus, 30 mg LFDT was proved to be bioequivalent to 30 mg LPZ capsule. Although ANOVA was also applied to Tmax, MRT, AUC0-100 and Cmax, no significant differences were found out in any of the parameters. Therefore, LFDT and LPZ capsule were proved to be bioequivalent.

As a conclusion, a novel fast disintegrating LPZ tablet shows the same serum LPZ concentration vs. time curves as the conventional LPZ capsule. The mean Cmax and Tmax are 992.8 ± 384.3 ng/mL and 1.91 ± 0.88 h, respectively. After the oral administration of LFDT, it disintegrates fast in the subjects’ mouths. However, 100.78 ± 2.28% of the administered LPZ were recovered into the saliva. In addition, serum LPZ concentration was very low or was not detected.

References


