Regular Article

*Influence of Itraconazole Co-administration and CYP2D6 Genotype on the Pharmacokinetics of the New Antipsychotic ARIPIPRAZOLE*

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Summary: The results of *in vitro* studies indicated that ARIPIPRAZOLE, a newly developed antipsychotic, is mainly metabolized by the human cytochrome P450 isozymes CYP3A4 and CYP2D6. The objective of the present study was to investigate the influence of itraconazole (hereafter referred to as ITZ) co-administration (CYP3A4 inhibition) on the pharmacokinetics of ARIPIPRAZOLE administered to 24 healthy adult male volunteers in a fasting condition. The influence of CYP3A4 inhibition was also examined by CYP2D6 genotype.

All subjects were administered a single oral dose of ARIPIPRAZOLE alone in Period I and a single oral dose of ARIPIPRAZOLE following administration of ITZ at 100 mg/day for 7 consecutive days in Period II. The pharmacokinetic parameters of ARIPIPRAZOLE and its main metabolite OPC-14857 were determined.

Co-administration of ITZ increased the Cmax, AUC0–24 hr, and t1/2, z of ARIPIPRAZOLE and OPC-14857 by 19.4%, 48.0%, and 18.6% and by 18.6%, 38.8%, and 53.4%, respectively. By co-administration of ITZ, the CL/F of ARIPIPRAZOLE in extensive metabolizers was decreased by 26.6%, with an even greater decrease (47.3%) in intermediate metabolizers. For the co-administration period, the CL/F of ARIPIPRAZOLE in intermediate metabolizers was about half of that in extensive metabolizers. For Cmax, there was no significant difference between extensive metabolizers and intermediate metabolizers, and the percent change by co-administration of ITZ was less than 20% in both extensive metabolizers and intermediate metabolizers.

For OPC-14857, the tmax in intermediate metabolizers was longer than that in extensive metabolizers, with the difference being amplified by co-administration of ITZ. The AUC0–24 hr showed similar increases by co-administration of ITZ in all genotypes. The urinary 6β-hydroxycortisol/cortisol concentration ratio following ITZ administration for 7 consecutive days was about half of that before the start of ITZ administration, indicating that CYP3A4 metabolic activity was inhibited by administration of ITZ. The influence of CYP3A4 inhibition on the pharmacokinetics of ARIPIPRAZOLE was not considered to be clinically significant. On the other hand, definite differences in pharmacokinetics were observed between CYP2D6 genotypes.

Key words: ARIPIPRAZOLE; pharmacokinetics; CYP3A4 inhibition; CYP2D6 genotypes

Introduction

In recent years the investigation of drug interaction has come to be essential for appropriate evaluation of the safety and efficacy of drugs and for appropriate use of drugs after market launch. Especially in the psychiatric field, where it is quite common to provide multiple-drug combination therapy, obtaining adequate information on drug interaction becomes very important.
ARIPIPRAZOLE (chemical structure shown in Fig. 1) is a new antipsychotic developed by Otsuka Pharmaceutical Co., Ltd.1) The results of in vitro studies indicated that ARIPIPRAZOLE is mainly metabolized by the human cytochrome P450 isozymes CYP3A4 and CYP2D6.2) It has been reported that CYP3A4 and CYP2D6 are the metabolic enzymes for numerous compounds and also that there are many compounds that inhibit these enzymes.

Although individual differences in hepatic levels of CYP3A4 enzyme protein have been reported to vary as much as 40 fold,3) almost no gene mutations affecting CYP3A4 metabolic activity or ethnic differences have been reported. For CYP2D6, however, a number of polymorphisms and the existence of ethnic differences in the types and distribution of polymorphisms have been reported.3,4) Therefore, it was considered important to investigate the pharmacokinetics of ARIPIPRAZOLE in Japanese subjects when CYP2D6 becomes the main metabolic enzyme as a result of co-administration of a CYP3A4 inhibitor.

Considering the above-mentioned points, the present study was planned for the purpose of investigating the influence of CYP3A4 inhibition on the pharmacokinetics of ARIPIPRAZOLE.

As mentioned above, the metabolic activity of CYP2D6 was expected to influence the pharmacokinetics of ARIPIPRAZOLE when CYP3A4 was inhibited by ITZ. In the present study, therefore, CYP2D6 genotyping of each subject was performed and the influence of CYP3A4 inhibition on the pharmacokinetics of ARIPIPRAZOLE was examined by CYP2D6 genotype.

In addition, the pharmacokinetics of OPC-14857 (chemical structure shown in Fig. 1), which is the main metabolite of ARIPIPRAZOLE in humans, were also evaluated, since the results of pharmacological studies indicated that OPC-14857 has pharmacological activity equivalent to that of ARIPIPRAZOLE and the results of preclinical studies indicated that CYP3A4 is involved in the production and elimination of OPC-14857.2)

As the urinary 6β-hydroxy cortisol/cortisol concentration ratio is known to be an indicator of CYP3A4 metabolic activity,5) the inhibition of CYP3A4 metabolic activity by ITZ was confirmed by comparing the urinary 6β-hydroxy cortisol/cortisol concentration ratio between before and after ITZ administration.

**Methods**

**Study design and subjects:** This study was designed as an open-label add-on study in reference to the Guidance for Drug Interaction Studies (Notification No. 813 issued by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare of Japan, on June 4, 2001). As an inhibitor of CYP3A4 metabolic activity, ITZ (Itrizole® Capsule 50, Janssen Pharmaceutical) was chosen from the in vivo CYP3A4 inhibitors listed in the aforementioned Notification No. 813, since the product is an oral formulation and has a lower incidence of serious adverse reactions than other CYP3A4 inhibitors. The dose of ITZ in the present study was set at 100 mg a day, as it has been reported that administration of ITZ at a clinical dose of 100 mg inhibits CYP3A4 metabolic activity.7,8)

This study was completed in 24 healthy adult male volunteers. All subjects were administered a single dose of ARIPIPRAZOLE alone in Period I (administration alone period) and a single dose of ARIPIPRAZOLE during steady-state administration of the CYP3A4 inhibitor ITZ in Period II (co-administration period). ARIPIPRAZOLE was orally administered at 3 mg once under a fasting condition on the 1st day of each period (Periods I and II). ITZ was administered at 100 mg/day once daily after breakfast for 21 consecutive days from 7 days before to the 14th day after Period II administration of ARIPIPRAZOLE, except on the day of ARIPIPRAZOLE administration, when the two drugs were co-administered under a fasting condition. The washout period between ARIPIPRAZOLE administration in Period I and the start of ITZ administration was 35 days.

Subjects were admitted to the study site from the day before ARIPIPRAZOLE administration to the 4th day of Period I (5 days) and from 2 days before the start of ITZ administration to the 4th day of Period II (13 days).

Prior to the screening examination, the principal investigator or attending investigator gave each subject a full explanation of the study using the informed consent form and written information for subjects and obtained consent from each subject in writing.

Demographic and other baseline characteristics for the population for analysis of the influence of CYP3A4 inhibition (n = 24) are shown in Table 1.

**Procedures:** This clinical study was conducted at the
Research Institute of Osaka Pharmacology Research Clinic. The subjects, all of whom were judged to be eligible for the study after a screening examination, were required to abstain from food and beverages from the completion of dinner on the day before ARIPIPRAZOLE administration until 4 hr postdosing in each period (Periods I and II).

Venous blood sampling (5 mL) for determination of plasma drug concentrations was performed 15 times each in Periods I and II (at 2 hr before and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 144, 240, and 336 hr after ARIPIPRAZOLE administration) and once at 2 hr before the start of ITZ administration, for a total of 31 timepoints. Venous blood (10 mL) for CYP2D6 genotyping was also collected from each subject prior to ARIPIPRAZOLE administration in Period I.

To confirm that CYP3A4 was inhibited by ITZ by using the urinary 6β-hydroxycortisol/cortisol concentration ratio as an indicator, urinary cortisol and 6β-hydroxycortisol concentrations were measured in cumulative 24-hr urine collected on the day before ITZ administration and on the 7th day of ITZ administration (day before Period II ARIPIPRAZOLE administration).

During the study period, subjects were instructed to adhere to the following restrictions: 1) to abstain from food and beverages other than that provided at the study site from dinner on the day of admission until discharge, 2) to abstain from consuming grapefruit or grapefruit products from 1 week before the first ARIPIPRAZOLE administration until completion of examinations on the 15th day of Period I and from 1 week before the start of ITZ administration until completion of examinations on the 15th day of Period II, since such substances have been reported to inhibit CYP3A4 drug-metabolizing enzyme activity,9 and 3) to abstain from consuming dietary supplements containing Saint John’s Wort from 2 weeks before the first ARIPIPRAZOLE administration until completion of examinations on the 15th day of Period I and from 2 weeks before the start of ITZ administration until completion of examinations on the 15th day of Period II, since that substance has been reported to stimulate CYP3A4 drug-metabolizing enzyme activity.

CYP2D6 genotyping: For CYP2D6 genotyping, 10 mL of venous blood was collected from each subject using a heparinized blood collection tube before Period I ARIPIPRAZOLE administration and CYP2D6 genotypes were examined using PCR-RFLP and Long-PCR methods. Genotyping was performed for CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*14, CYP2D6*18, and CYP2D6*36, and all genotypes other than those were regarded as CYP2D6*1. CYP2D6 genotypes were classified into the following 5 categories according to the anticipated metabolic enzyme activity of the genotype.

1) Extensive metabolizer: CYP2D6 genotype identified as homozygous *1 or a zygote of *1 and some other active allele (*1/*1, *1/*10, etc.)
2) Intermediate metabolizer: CYP2D6 genotype identified as a zygote of *10 and some other allele except *1 and *2 (*5/*10, *10/*10, etc.)
3) Poor metabolizer: CYP2D6 genotype identified as a homo- or heterozygote of a defective gene (*4/*4, *5/*5, *4/*5, etc.)
4) *2 Group: CYP2D6 genotype identified as a homo- or heterozygote of *2 (*1/*2, *2/*2, *2/*5, *2/*10, etc.). These alleles were all classified as *2 Group because a CYP2D6*2 variant assigned as CYP2D6*41 (decreased activity) was reported after genotyping was performed in this study and the activities of these zygotest including CYP2D6*2 could not be assessed.
5) Other: CYP2D6 genotype other than those above (*1/*5, etc.)

For performing the CYP2D6 genotyping and the handling of data obtained in the study, reference was made to “Fundamental Principles of Research on the Human Genome” issued by the Bioethics Committee, Council of Science and Technology, on June 14, 2000, and to “Ethical Principles of Human Genome Research and Gene Analysis” jointly issued by the MHLW, the Ministry of Education, Culture, Sports, Science, and Technology, and the Ministry of Economy, Trade, and Industry on March 29, 2001.

Determination of plasma drug concentrations: Plasma concentrations of ARIPIPRAZOLE and its main metabolite OPC-14857 were determined from 0.4 mL of plasma by Sumika Chemical Analysis Service, Ltd., using LC-MS/MS (liquid chromatography tandem mass spectrometry).

The lower limit of quantitation (LLOQ) for both analytes was set at 0.1 ng/mL. For the concentration range of 0.1 to 100 ng/mL, intra-assay precision was <5.1% CV for ARIPIPRAZOLE and <15.9% CV for OPC-14857.

Determination of urinary cortisol and 6β-Hydroxycortisol concentrations: Cumulative 24-hr urine samples were mixed well and aliquots were prepared and kept frozen until transfer to the laboratory. Urinary cortisol and 6β-hydroxycortisol concentrations were measured

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**Table 1.** Demographic and other baseline characteristics (population for analysis: n = 24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>23.2</td>
<td>2.4</td>
<td>21</td>
<td>22.5</td>
<td>32</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.90</td>
<td>6.12</td>
<td>161.7</td>
<td>173.25</td>
<td>184.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.76</td>
<td>5.44</td>
<td>50.9</td>
<td>62.15</td>
<td>73.7</td>
</tr>
</tbody>
</table>

Influence of CYP3A4 Inhibition on PK of ARIPIPRAZOLE 57
by Daiichi Pure Chemicals Co., Ltd., using LC-MS/MS.

The precision and accuracy of the system for the determination of cortisol and 6β-hydroxycortisol were examined using cortisol samples at 10, 20, and 100 ng/mL and 6β-hydroxycortisol samples at 50, 100, and 500 ng/mL. Precision and accuracy ranged from 0.0% to 10.0% and from −10.0% to 0.0%, respectively, and those values satisfied the quality standards (±20% for precision and ±20% for accuracy).

**Pharmacokinetic analysis:** Pharmacokinetic parameters of ARIPIPRAZOLE (Cmax, tmax, AUC336 hr, AUC20, t1/2,α, and CL/F) and OPC-14857 (Cmax, tmax, AUC336 hr, AUC20, and t1/2,α) were calculated for each subject by a noncompartmental method using WinNonlin® (Ver. 3.3, Pharsight Corporation).

**Statistical analysis:** Descriptive statistics (mean and standard deviation) of the plasma concentrations of ARIPIPRAZOLE and OPC-14857 at 10, 20, and 100 ng/mL and 6β-hydroxycortisol at 50, 100, and 500 ng/mL were summarized by CYP2D6 genotype.

Descriptive statistics of each pharmacokinetic parameter of ARIPIPRAZOLE and OPC-14857 were calculated for Period I (ARIPIPRAZOLE alone) and Period II (co-administration with ITZ) by genotype. Descriptive statistics of the Period I/II ratio for each parameter were also calculated.

To evaluate the differences between the mean values of each pharmacokinetic parameter by CYP2D6 genotype, analysis of variance (one-way ANOVA) and Fisher’s least significant difference test were performed.

For analysis of the influence of CYP3A4 inhibition, descriptive statistics of the ratio and difference of each pharmacokinetic parameter between administration of ARIPIPRAZOLE alone and for co-administration of ARIPIPRAZOLE with ITZ were calculated and Student’s paired t-test was performed with α=0.05.

Descriptive statistics of the urinary 6β-hydroxycortisol/cortisol concentration ratio, and the ratio between the concentration ratio on the day before the start of ITZ administration and that on the 7th day of ITZ administration (final day of administration of ITZ alone) were calculated and Student’s paired t-test was performed.

**Results**

**Study subjects:** In CYP2D6 genotyping, 14 subjects were classified as extensive metabolizers (4 for *1/*1 and 10 for *1/*10), 3 as intermediate metabolizers (*10/*10), 4 as *2 Group (*2/*10), and 3 as “Other” (*1/*5). There were no subjects classified as poor metabolizers.

**Pharmacokinetic analysis:** The pharmacokinetic parameters of ARIPIPRAZOLE and OPC-14857 were compared between Period I (administration alone period) and Period II (co-administration period). The major pharmacokinetic parameters of ARIPIPRAZOLE and OPC-14857 by CYP2D6 genotype are respectively shown in Table 2 and Table 3.

Of the mean pharmacokinetic parameters of ARIPIPRAZOLE in all subjects, CL/F was decreased by 32.5% and Cmax, AUC336 hr, and t1/2,α were respectively increased by 19.4%, 48.0%, and 18.6% by co-administration of ITZ. Of the mean pharmacokinetic parameters of OPC-14857 in all subjects, Cmax, AUC336 hr, and t1/2,α were respectively increased by 18.6%, 38.8%, and 53.4% by co-administration of ITZ. All of those changes were judged to be statistically significant by paired t-test.

The timecourses of the mean plasma concentrations of ARIPIPRAZOLE and OPC-14857 are shown in Fig. 2.

The ratio of the t1/2,α of OPC-14857 between the administration alone period and the co-administration period could not be determined in 9 subjects because linearity for at least 3 points could not be obtained in the terminal phase for the co-administration period.

Regarding total exposure, the combined AUC336 hr of ARIPIPRAZOLE and OPC-14857 was increased by approximately 45% by co-administration of ITZ.

Analysis of variance (one-way ANOVA) was performed to investigate the relationship between the pharmacokinetic parameters of ARIPIPRAZOLE for Period I and the CYP2D6 genotype. Among those parameters, AUC and CL/F showed significant differences between CYP2D6*1/*1 and CYP2D6*10/*10.

The relationship between CL/F and CYP2D6 genotype is shown in Fig. 3. CL/F for *1/*10, *1/*5, and *2/*10 were similar to that for *1/*1 and no significant differences were observed. Data for CYP2D6*1/*5 is therefore included in extensive metabolizers in Table 2 and Table 3.

The timecourses of the mean plasma concentrations of ARIPIPRAZOLE and OPC-14857 by CYP2D6 genotype are shown in Fig. 4. In the comparison of pharmacokinetic parameters by CYP2D6 genotype, the mean plasma ARIPIPRAZOLE concentrations in intermediate metabolizers were higher than those in extensive metabolizers in both the administration alone period and the co-administration period. The CL/F of ARIPIPRAZOLE in extensive metabolizers was higher than that in intermediate metabolizers. The Cmax, tmax, AUC336 hr, and t1/2,α in extensive metabolizers were lower than those in intermediate metabolizers. By co-administration of ITZ, CL/F was decreased by 26.6% in extensive metabolizers and the change was statistically significant. Although the decrease in intermediate metabolizers was even greater (47.3%), the change was not judged to be statistically significant due to the small number of subjects. In the co-administration period, the
CL/F of ARIPIPRAZOLE in intermediate metabolizers was about half of that in extensive metabolizers. The difference in $C_{\text{max}}$ between extensive metabolizers and intermediate metabolizers and the changes in $C_{\text{max}}$ by co-administration of ITZ were both small.

Plasma OPC-14857 concentrations in intermediate metabolizers were lower than those in extensive metabolizers in both the administration alone period and the co-administration period (except at 336 hr postdosing). The $t_{\text{max}}$ of OPC-14857 in intermediate metabolizers was longer than that in extensive metabolizers, with the difference being amplified by co-administration of ITZ. The $C_{\text{max}}$ and $\text{AUC}_{336}^{\text{hr}}$ of OPC-14857 in extensive metabolizers were higher than those in intermediate metabolizers, and the increase in $\text{AUC}_{336}^{\text{hr}}$ by co-administration of ITZ was similar among all genotypes. The $t_{1/2,e}$ of OPC-14857 in the co-administration period could not be determined in 5 of 17 subjects classified as extensive metabolizers, all 3 subjects classified as intermediate metabolizers, and 1 of 4 subjects classified as *2 Group because linearity for at least 3 points could not be obtained in the terminal phase for the co-administration period.

**Urinary cortisol concentrations:** Descriptive statis-
Table 3. Major pharmacokinetic parameters of OPC-14857 by CYP2D6 genotype

<table>
<thead>
<tr>
<th>CYP2D6 genotype</th>
<th>Number</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (hr)</th>
<th>AUC&lt;sub&gt;0-24hr&lt;/sub&gt; (ng·hr/mL)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</th>
</tr>
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<tbody>
<tr>
<td>All Subjects</td>
<td></td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Period I</td>
<td>1.4 ± 0.3</td>
<td>57.0 ± 17.1</td>
<td>269 ± 74</td>
<td>92.9 ± 21.7</td>
<td></td>
</tr>
<tr>
<td>Period II</td>
<td>1.6 ± 0.5**</td>
<td>103.0 ± 62.7**</td>
<td>365 ± 103**</td>
<td>143.4 ± 65.4**</td>
<td></td>
</tr>
<tr>
<td>Ratio (II/I)</td>
<td>1.19 ± 0.26</td>
<td>46.0 ± 58.3**</td>
<td>1.39 ± 0.31</td>
<td>1.53 ± 0.52</td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>Number</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Period I</td>
<td>1.5 ± 0.3</td>
<td>56.6 ± 20.2</td>
<td>304 ± 72</td>
<td>93.9 ± 24.1</td>
<td></td>
</tr>
<tr>
<td>Period II</td>
<td>1.8 ± 0.3**</td>
<td>80.6 ± 36.0**</td>
<td>396 ± 78**</td>
<td>135.6 ± 74.4</td>
<td></td>
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<tr>
<td>(including *1/*5) Ratio (II/I)</td>
<td>1.17 ± 0.15</td>
<td>24.0 ± 33.9**</td>
<td>1.33 ± 0.22</td>
<td>1.42 ± 0.56</td>
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<tr>
<td>Intermediate</td>
<td>Number</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Period I</td>
<td>1.0 ± 0.1**</td>
<td>72.0 ± 0.0**</td>
<td>216 ± 26</td>
<td>—</td>
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<tr>
<td>Period II</td>
<td>1.1 ± 0.1</td>
<td>208.0 ± 110.9</td>
<td>291 ± 18</td>
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<tr>
<td>Ratio (II/I)</td>
<td>1.09 ± 0.11</td>
<td>136.0 ± 110.9**</td>
<td>1.36 ± 0.13</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>*1/*1</td>
<td>Number</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Period I</td>
<td>1.8 ± 0.2</td>
<td>42.0 ± 23.0</td>
<td>319 ± 71</td>
<td>75.4 ± 7.4</td>
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<tr>
<td>Period II</td>
<td>2.0 ± 0.3</td>
<td>78.0 ± 45.4</td>
<td>396 ± 97*</td>
<td>98.6 ± 9.8*</td>
<td></td>
</tr>
<tr>
<td>Ratio (II/I)</td>
<td>1.09 ± 0.06</td>
<td>36.0 ± 24.0**</td>
<td>1.24 ± 0.07</td>
<td>1.31 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>*1/*10</td>
<td>Number</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
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<tr>
<td>Period I</td>
<td>1.4 ± 0.2**</td>
<td>62.4 ± 16.8**</td>
<td>298 ± 75</td>
<td>100.9 ± 24.7</td>
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<tr>
<td>Period II</td>
<td>1.7 ± 0.3**</td>
<td>81.6 ± 34.3</td>
<td>396 ± 75**</td>
<td>149.5 ± 84.1</td>
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<tr>
<td>Ratio (II/I)</td>
<td>1.21 ± 0.16</td>
<td>19.2 ± 37.2**</td>
<td>1.36 ± 0.25</td>
<td>1.47 ± 0.67</td>
<td></td>
</tr>
<tr>
<td>*1/*5</td>
<td>Number</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Period I</td>
<td>1.1 ± 0.4**</td>
<td>56.0 ± 13.9</td>
<td>206 ± 70°</td>
<td>78.7</td>
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<tr>
<td>Period II</td>
<td>1.7 ± 1.1</td>
<td>120.0 ± 41.6</td>
<td>390 ± 229</td>
<td>170.0</td>
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<tr>
<td>Ratio (II/I)</td>
<td>1.55 ± 0.54</td>
<td>64.0 ± 36.7**</td>
<td>1.83 ± 0.53</td>
<td>2.16</td>
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<tr>
<td>*2/*10</td>
<td>Number</td>
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<td>4</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Period I</td>
<td>1.2 ± 0.3**</td>
<td>48.0 ± 0.0</td>
<td>233 ± 44</td>
<td>94.1 ± 16.8</td>
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<tr>
<td>Period II</td>
<td>1.2 ± 0.2</td>
<td>90.0 ± 36.0</td>
<td>295 ± 49</td>
<td>163.2 ± 31.3*</td>
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<tr>
<td>Ratio (II/I)</td>
<td>1.03 ± 0.23</td>
<td>42.0 ± 36.0**</td>
<td>1.30 ± 0.32</td>
<td>1.73 ± 0.13</td>
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</tbody>
</table>

—: Unable to be determined
Mean ± SD
*a* Difference (Period II-Period I)
**p < 0.01, *p < 0.05 (paired t-test vs. Period I)
**p < 0.01, *p < 0.05 (Fisher’s least significant difference test vs. *1/*1 in Period I)

The urinary 6β-hydroxycortisol/cortisol ratios are shown in Table 4 and the changes in urinary 6β-hydroxycortisol/cortisol ratios between before and after ITZ administration by individual subject are shown in Fig. 5.

In all subjects, the urinary 6β-hydroxycortisol/cortisol ratio was lower after ITZ administration. The ratio ranged from 3.74 to 9.82 (mean: 6.652) before the start of ITZ administration and from 1.72 to 6.67 (mean: 3.167) after repeated oral administration of ITZ for 7 consecutive days. The mean ratio decreased approximately 50% after administration of ITZ, and the change was judged to be statistically significant by Student’s paired t-test. The correlation coefficient between the postdosing/predosing ratio for the urinary 6β-hydroxycortisol/cortisol ratio and that for the CL/F of ARIPIPRAZOLE was 0.23, and no definite correlation was shown.

**Safety**

Regarding safety, there were no significant differences in the incidences of adverse events and adverse drug
reactions between administration of ARIPIPRAZOLE alone and co-administration with ITZ, and neither adverse events specific to co-administration with ITZ nor clinically significant issues for co-administration with ITZ were observed. It was thus considered that there were no clinically significant issues regarding the safety of ARIPIPRAZOLE when co-administered with itraconazole.

Discussion

1) Influence of CYP3A4 inhibition on the pharmacokinetics of ARIPIPRAZOLE

The purpose of this study was to investigate the influence of ITZ co-administration (CYP3A4 inhibition) on the pharmacokinetics of ARIPIPRAZOLE.

The inhibition of CYP3A4 metabolic activity by ITZ was confirmed using the urinary 6β-hydroxycortisol/cortisol concentration ratio as an indicator of CYP3A4 activity. Cumulative 24-hr urine was used for the assessment, since the urinary 6β-hydroxycortisol/cortisol concentration ratio is known to have a circadian rhythm. The urinary 6β-hydroxycortisol/cortisol
concentration ratio decreased by co-administration of ITZ in all subjects, with a mean decrease of 51%. The changes in the urinary 6β-hydroxycortisol/cortisol concentration ratio are considered to have indicated inhibition of CYP3A4 by ITZ, and the determination of the urinary 6β-hydroxycortisol/cortisol concentration ratio is considered to be meaningful as an indicator of CYP3A4 inhibition.

A weak correlation (correlation coefficient: 0.23) was observed between the postdosing/predosing ratio for the urinary 6β-hydroxycortisol/cortisol ratio and that for the CL/F of ARIPIPRAZOLE, and no significant difference in the postdosing/predosing ratio for the urinary 6β-hydroxycortisol/cortisol ratio was observed among CYP2D6 genotypes.

Plasma concentrations of ARIPIPRAZOLE and its main metabolite OPC-14857 in the elimination phase in the co-administration period were higher than those for the administration alone period, and t1/2 was delayed by co-administration of ITZ. The increase in plasma ARIPIPRAZOLE concentration and the delay in t1/2 by co-administration of a CYP3A4 inhibitor indicated decreased hepatic clearance, since almost no ARIPIPRAZOLE or OPC-14857 was excreted in the urine. This result demonstrated that CYP3A4 is involved in the metabolism of ARIPIPRAZOLE, which
Influence of CYP3A4 Inhibition on PK of ARIPIPRAZOLE

is consistent with the results of an in vitro study.\textsuperscript{2)}

ARIPIPRAZOLE is known to have good absorption from the gastrointestinal tract, and absolute bioavailability is 87%.\textsuperscript{2)} Therefore, the influence of CYP3A4 in the gastrointestinal tract on the pharmacokinetics of ARIPIPRAZOLE during the absorption phase is relatively small. The \( t_{\text{max}} \) of ARIPIPRAZOLE was about 3 hr, indicating that absorption from the gastrointestinal tract was relatively fast.

The plasma concentration of OPC-14857 during the later phase of elimination was increased in the co-administration period, and the production of OPC-14857 from ARIPIPRAZOLE was considered to be inhibited by co-administration of ITZ. This also indicated that the metabolism of OPC-14857 was inhibited by CYP3A4 inhibition. The delayed increase in the plasma OPC-14857 concentration and the associated delay in \( t_{\text{max}} \) in the co-administration period were consistent with the results expected from the decreased rate of production of OPC-14857 from ARIPIPRAZOLE.

2) Pharmacokinetics of ARIPIPRAZOLE by CYP2D6 genotype

In the ARIPIPRAZOLE administration alone period, plasma ARIPIPRAZOLE concentrations in intermediate metabolizers were higher than those in extensive metabolizers. On the other hand, plasma OPC-14857 concentrations in intermediate metabolizers were lower than those in extensive metabolizers. The tendencies observed in the present study were similar to those observed in a comparison of pharmacokinetics by CYP2D6 genotype in another single dosing study of ARIPIPRAZOLE at 6-mg in healthy adult male volunteers (submitted for publication).

For the ITZ co-administration period in the present study, plasma ARIPIPRAZOLE concentrations in intermediate metabolizers were higher than those in extensive metabolizers, while the increases in plasma OPC-14857 concentrations in intermediate metabolizers were smaller and slower than those in extensive metabolizers. The extent of decrease in the elimination rates for the ARIPIPRAZOLE and OPC-14857 plasma concentrations by co-administration of ITZ was greater in intermediate metabolizers than in extensive metabolizers. Therefore, the influence of CYP3A4 inhibition on the elimination rate was considered to be greater in intermediate metabolizers than in extensive metabolizers.

In subjects classified as *2 Group, the pharmacokinetics more closely resembled those in extensive metabolizers than those in intermediate metabolizers. It was thus assumed that there were no CYP2D6*41 subjects in the group.

In a drug interaction study in which ARIPIPRAZOLE was co-administered with quinidine (a CYP2D6 inhibitor) in healthy volunteers in the US,\textsuperscript{2)} the CL/FBW of ARIPIPRAZOLE in CYP2D6 extensive metabolizers was decreased by approximately 50\% (from 45.6 mL/hr/kg to 22.0 mL/hr/kg) by co-administration of quinidine, and a similar CL/FBW was seen in poor metabolizers (27.0 mL/hr/kg). The results of that study indicated that CYP2D6 was almost completely inhibited by quinidine. Using the data for CL/FBW in extensive metabolizers and poor metabolizers, the ratio of hepatic clearance of ARIPIPRAZOLE by CYP3A4 and CYP2D6 in CYP2D6 extensive metabolizers was estimated to be approximately 1:1.

Assuming that the ratios of hepatic clearance in CYP2D6 extensive metabolizers in the US and Japan are similar and that the ratio of hepatic clearance by CYP3A4 between CYP2D6 extensive metabolizers and CYP2D6 poor metabolizers is also similar, the ratio of hepatic clearance of ARIPIPRAZOLE by CYP3A4 and CYP2D6 in intermediate metabolizers is estimated to be
3:1 (2.3 L/hr vs. 0.8 L/hr). Using the data for the decrease in the hepatic clearance of ARIPIPRAZOLE by co-administration of ITZ (1.35 L/hr in extensive metabolizers and 1.44 L/hr in intermediate metabolizers), the decrease in hepatic clearance by CYP3A4 was estimated to be approximately 60% (from 2.3 L/hr to 0.9 L/hr) in both CYP2D6 extensive metabolizers and CYP2D6 intermediate metabolizers.

These results indicated that in CYP2D6 extensive metabolizers, CYP2D6 and CYP3A4 are approximately equally responsible for the metabolism of ARIPIPRAZOLE, OPC-14857 is the main metabolite produced, and CYP3A4 is the main metabolic enzyme involved in the metabolism of OPC-14857.

In conclusion, when administered at clinical doses, ITZ, which is known to strongly inhibit CYP3A4, would increase the AUC of ARIPIPRAZOLE by 50% at maximum, which is unlikely to cause clinically significant issues.

References