Steady-State Pharmacokinetic Properties of Aripiprazole 10 mg PO q12h in Han Chinese Adults with Schizophrenia: A Prospective, Open-Label, Pilot Study

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ABSTRACT

Objectives: The aims of this study were to investigate the pharmacokinetic (PK) properties of aripiprazole in the steady state in Han Chinese adults with schizophrenia and to compare them between Han Chinese and white populations described in the literature.

Methods: This prospective, open-label, pilot study was conducted at the Mental Health Institute, Xiang-ya Second Hospital, Central South University, Changsha, China. Male and female hospitalized patients aged 18 to 45 years diagnosed with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)–defined schizophrenia, with a Positive and Negative Syndrome Scale (PANSS) total score >60 (indicating schizophrenia of at least mild severity) were eligible. On study days 1 and 2, patients were pretreated with aripiprazole 10 mg PO QD, followed by 10 mg q12h on days 3 to 21. Blood samples were drawn for analysis on day 21 before dosing and 1, 3, 4, 5, 12, 24, 48, 72, 96, 144, and 192 hours after the morning dosing of aripiprazole on day 21. Patients received low-dose (25–100 mg/d) clozapine on day 25 until day 28. The samples were assessed using high-performance liquid chromatography–mass spectrometry and compartment model analysis for aripiprazole. PK properties included mean residence time (MRT), steady-state Cmax (Css max), time to Css max (Tmax), elimination t1/2, apparent oral clearance (CL/F), and apparent volume of distribution (V/F). Adverse effects were monitored using physical examination (including vital sign measurements), electrocardiography, electroencephalography, and clinical laboratory testing (including biochemistry, hematology, and urinalysis) at baseline and at the end of the study. Patients were asked about adverse events on days 1 to 7 and at random intervals thereafter.

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Patients were also instructed to report any spontaneous symptoms they experienced.

**Results:** Twelve patients were enrolled (6 men, 6 women; mean [SD] age, 26.1 [7.0] years; mean [SD] weight, 56.6 [9.0] kg; mean [SD] PANSS score, 116.8 [12.2]). Aripiprazole exhibited linear kinetic characteristics on a 2-compartment model. After multiple oral doses (10 mg q12h), the mean (SD) \( t_{1/2} \), \( C_{ss \text{ max}} \), \( T_{\text{max}} \), MRT, V/F, and CL/F were 62.2 (9.0) hours, 557.3 (135.5) ng/mL, 2.6 (1.1) hours, 84.5 (11.2) hours, 173 (48) L, and 1.9 (0.5) L/h, respectively. In Chinese patients, the \( t_{1/2} \) values were numerically similar (62.2 [9.0] vs 68.1 [22.9] hours); \( C_{ss \text{ max}} \) values were numerically higher (557.3 [135.5] vs 393 [181] ng/mL); and V/F and CL/F values were numerically lower (V/F: 173 [48] vs 196 [66] L; CL/F: 1.9 [0.5] vs 3.4 [1.6] L/h) compared with healthy white male volunteers. Adverse effects were mild to moderate: lightheadedness (5 of 12 patients), somnolence (3), tachycardia (3), hypodynamia (2), and extrapyramidal symptoms (EPS) (1). The EPS (convulsive movement of the muscles related to the larynx) led to one patient's discontinuation of the study.

**Conclusions:** In this small pilot study of the PK properties of aripiprazole 10 mg PO q12h in Han Chinese patients with schizophrenia, the mean \( t_{1/2} \) value was numerically similar to that previously reported in a population of healthy white male volunteers. However, the mean \( C_{ss \text{ max}} \) value was numerically higher, and V/F and CL/F values were numerically lower, compared with those in healthy white male volunteers. (Curr Ther Res Clin Exp. 2006;67:258-269) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** aripiprazole, pharmacokinetics, schizophrenic, Chinese.

**INTRODUCTION**

Aripiprazole, an oral psychotropic, is a quinolinone derivative with a pharmacologic profile that differs from other currently available typical and atypical antipsychotics. Aripiprazole demonstrates mixed dopamine-2 (D2) and serotonin (5-HT) 1A receptor agonist–antagonist activity that is hypothesized to improve positive and negative symptoms of schizophrenia. As a partial agonist, aripiprazole is postulated to stabilize the dopaminergic system, improving the symptoms of schizophrenia without producing unwanted antagonist activity associated with adverse effects, such as extrapyramidal symptoms (EPSs) and hyperprolactinemia. Aripiprazole also has been found to have partial agonist activity at the 5-HT1A receptor and antagonistic activity at the 5-HT2A receptor. It has been postulated that partial agonist activity at the 5-HT1A receptor might contribute to improvement in anxiety, depression, negative symptoms (eg, apathy, lack of interpersonal communications, lack of drive), and fewer EPSs. Aripiprazole has been found to have efficacy measured by Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions (CGI)-Severity of Illness, and mean CGI-Improvement scores in short- (4 weeks) and long-term (26 and 52 weeks) clinical studies involving patients with schizo-
Phrenia or schizoaffective disorders. Aripiprazole treatment was found to be well tolerated in those studies, with a low risk for EPSs (3%-10%), weight gain (5%-14%), and hyperprolactinemia (3.4%).

Aripiprazole is well absorbed, with $C_{\text{max}}$ plasma occurring within 3 to 5 hours with the absolute oral bioavailability of the tablet formulation being 87%. Aripiprazole can be administered with or without food. In vitro data suggest that aripiprazole is extensively metabolized via the hepatic cytochrome P-450 (CYP) 3A4 and CYP2D6 isozyme pathways. Mean $t_{1/2}$ values have been found to be 75 and 94 hours for aripiprazole and the active metabolite, dehydroaripiprazole, respectively. Steady-state plasma concentrations are attained within 14 days of the start of treatment for aripiprazole and dehydroaripiprazole.

Mallikaarjun et al reported the results from 2 randomized, placebo-controlled, double-blind studies that assessed the pharmacokinetic (PK) properties and tolerability of aripiprazole at 5 mg/d, and 10, 15, and 20 mg/d in 39 healthy male volunteers. The 2 studies found that aripiprazole had a linear PK profile over the 5- to 30-mg/d dose range studied. Steady state $C_{\text{max}}$ ($C_{\text{ss maxi}}$) (day $\geq$14), ranged from 98 to 452 ng/mL, with corresponding time to $C_{\text{ss maxi}}$ ($T_{\text{maxi}}$) values of 3 to 5 hours, respectively. The terminal $t_{1/2}$ ranged from 48 to 68 hours across doses. A randomized, double-blind, parallel-group, inpatient, pilot study by Auby et al in a white population found that the $C_{\text{ss maxi}}$ of aripiprazole and its metabolites increased proportionately with dose, but no detailed PK properties were reported.

Although the PK properties of aripiprazole have been reported in healthy white male volunteers, aripiprazole has been found to have large between-subject PK variability. Based on a MEDLINE/PubMed search of the literature (key terms: aripiprazole, Han Chinese, schizophrenic, and pharmacokinetics; years: 1990-2006), data comparing the PK properties of aripiprazole in schizophrenic patients versus healthy volunteers are limited. In addition, although a PK assessment of aripiprazole found no evidence of clinically significant race-related differences, the aripiprazole PK properties in Han Chinese patients with schizophrenia have not been reported. Therefore, the aims of the present study were to investigate the PK properties of aripiprazole at the steady state in Han Chinese patients with schizophrenia and compare them between Han Chinese and white male populations described in the literature.

**PATIENTS AND METHODS**

This prospective, open-label, pilot study was conducted at the Mental Health Institute, Xiang-ya Second Hospital, Central South University, Changsha, China. The local ethics committee reviewed and approved the study protocol. Written informed consent was obtained from all patients before involving them in any study-related procedures. This study complied with the principles of the Guideline for Good Clinical Practice and the World Medical Association's Declaration of Helsinki and its amendments.
**Inclusion and Exclusion Criteria**

Male and female hospitalized Han Chinese patients aged 18 to 45 years, with body weight within 10% of ideal (which was calculated using the following formula: [height (cm) - 80] × 0.7 kg for men and [height (cm) - 70] × 0.6 kg for women\(^1\)) and with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*\(^7\) defined diagnosis of schizophrenia with a PANSS\(^6\) total score ≥60 (indicating schizophrenia of at least mild severity) were eligible. The PANSS is an interview-based assessment of the severity of positive, negative, and general psychopathology in adults with schizophrenia, composed of 3 scales and 30 items (positive scale, 7 items; negative scale, 7 items; general psychopathology scale, 16 items), with individual items rated on an anchored scale of 1 (absent) to 7 (extreme) (scale: <90 = mild; 90-119 = moderate; 120-150 = severe).\(^6\)

Patients with any of the following criteria were excluded from the study: presence of cardiovascular disease, hepatic abnormalities, renal disorder, digestive tract disease, or other concurrent medical conditions that might interfere with the assessment; treatment with any inhibitor or inducer of CYP3A4 (eg, ketoconazole, carbamazepine) or CYP2D6 (eg, quinidine, fluoxetine, paroxetine)\(^1\) in the previous 2 weeks; treatment failure with clozapine; treatment with any concomitant medications that might interfere with the metabolism of aripiprazole; in women, pregnancy or breastfeeding; a positive test for drugs of abuse on urinalysis; history of alcohol abuse, illicit drug abuse, or drug allergy; a smoking habit; a positive test for HIV; donation of blood or plasma in the previous 90 days; and/or participation in another investigational drug study within the previous 30 days.

**Study Drug Administration**

Patients were enrolled and received pretreatment on study days 1 and 2 with aripiprazole 10 mg PO QD, followed by aripiprazole 10 mg q12h (7 AM and 7 PM) on days 3 to 21. Patients were hospitalized throughout the treatment period. On day 25, aripiprazole was replaced by low-dose (25-100 mg/d) clozapine until day 28 for determination of the \(t_{1/2}\) of aripiprazole.

**Blood Sampling**

Blood samples for PK analysis were drawn by a nurse before dosing on day 21 and at 1, 3, 4, 5, 12, 24, 48, 72, 96, 144, and 192 hours after the morning dosing of aripiprazole on day 21. To assess the steady-state of aripiprazole, blood samples were drawn before the morning dose on days 18 through 20. The samples were collected in disposable ethylenediaminetetraacetic acid tubes and left at room temperature (25°C) for not longer than 1 hour and then centrifuged at 3000g for 5 minutes. The plasma was transferred to plastic tubes and stored frozen at −80°C until analysis.

**Bioanalytic Methods**

Plasma aripiprazole concentrations were determined using high-performance liquid chromatography–electrospray mass spectrometric (HPLC-MS) assay
CURRENT THERAPEUTIC RESEARCH

(Waters 2690 Micromass ZQ, Wythenshawe, Manchester, United Kingdom; Hypersil Gold C18 column, Thermo Electron Corporation, Waltham, Massachusetts). Plasma samples containing aripiprazole were prepared for analysis by the addition of methanol (Tedia Company Inc., Fairfield, Ohio)-containing internal standard (estazolam [purity, 99.9%], National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China). Extraction and chromatography were based on the published method of Kubo et al. Plasma samples were vortexed briefly and aliquots (150 μL) were transferred to glass centrifuge tubes, then alkalinized by the addition of 30 μL aqueous ammonia (Hunan Chemical Reagent Factory, Changsha, China). Methyl-t-butyl ether (Tedia Company Inc.) 4 mL as extractant was added to the samples. Supernatant was transferred to a clean tube and evaporated in nitrogen in a 50°C water bath. The residue was dissolved in 150 μL of mobile phase containing 0.1% trifluoroacetic acid (Hunan Chemical Reagent Factory). Five microliters of sample were injected into the HPLC-MS system, with acetonitrile (Tedia Company Inc.) 30-mmol/L ammonium acetate containing 0.1% formic acid, 58:42 (v/v), as mobile phase. The protonated analyte was quantified by selected ion recording with a quadrupole mass spectrometer (Waters 2690 Micromass ZQ) in positive-ion mode. Target ions were monitored at 448 and 450 m/z (the mass/charge ratio) for aripiprazole and 295 m/z for estazolam. Calibration plots were linear over the concentration range of 19.9 to 1119.6 ng/mL. The lower limit of quantization was 19.9 ng/mL. Intraday and interday precision (CV%) and accuracy (RE%) for the 3 quality-control plasma samples (37.3, 124.4, and 622.0 ng/mL, respectively) (Blood Center, Shanghai, China) ranged between 2.5% and 9.0% and between 1.3% and 3.5%, respectively. Extraction recovery of aripiprazole from plasma was in the range of 75.8% to 84.1%. Plasma aripiprazole concentrations were determined in the laboratory at the hospital.

Pharmacokinetic Calculation

The plasma concentration–time curves for each patient were analyzed using 3P97 software (Chinese Pharmacological Society and the Mathematic and Pharmaco-Professional Committee, Beijing, China). This model was based on all plasma concentrations collected on days 21 to 28. The PK compartment model that best fit the data was selected based on goodness of fit (r²) and the Akaike information criterion.

Following oral administration, a 2-compartment open model was found to best fit the data with the biexponential equation

\[ C = Ne^{-k_a t} + Le^{-\alpha t} + Me^{-\beta t}, \]

where \( C \) is the plasma aripiprazole concentration; \( N \) and \( k_a \) are the intercept and slope, respectively, of the absorption phase; \( L \) and \( \alpha \) are the intercept and slope, respectively, of the distribution phase; \( M \) and \( \beta \) are the intercept and slope, respectively, of the elimination phase; and \( t \) is time. The \( t_{1/2} \) of the \( k_a \) phase (\( t_{1/2} k_a \)).
$\alpha$ phase ($t_{1/2}^\alpha$), and $\beta$ phase ($t_{1/2}^\beta$); mean residence time (MRT); distribution rate constant for drug transfer from the central to peripheral compartment ($k_{12}$); transfer rate constant from peripheral to central compartment ($k_{21}$); and elimination rate constant ($k_{10}$) were calculated using the 3P97 software. Values for steady-state $C_{\text{min}}$ ($C_{\text{ss min}}$), steady-state $C_{\text{max}}$, and time to $C_{\text{ss max}}$ were determined from the observed data. After study drug administration on day 21, the steady-state AUCs from time 0 to 12 hours (AUC$_{\text{ss 0-12}}$), 0 to 192 hours (AUC$_{\text{ss 0-192}}$), and 0 to infinity (AUC$_{\text{ss 0-\infty}}$) were calculated using a trapezoidal method. The mean plasma concentration for the 12-hour drug administration interval ($C_{\text{ss av}}$) was calculated using the equation $C_{\text{ss av}} = $ AUC$_{\text{ss 0-12}}/12$. The oral clearance at steady state (CL/F) was calculated using the equation $CL/F = 10 \text{ mg}/(\text{AUC}_{\text{ss 0-12}})$. The apparent volume of distribution (V/F) was calculated as $V/F = CL/\beta$. The fluctuation percentage (Fl) was calculated as $Fl = (\lceil C_{\text{ss max}} \rceil - \lceil C_{\text{ss min}} \rceil)/(C_{\text{ss max}})$.

**Tolerability Assessment**

Adverse effects were monitored using physical examination (including vital sign measurements), electrocardiography, electroencephalography, and clinical laboratory testing (including biochemistry, hematology, and urinalysis) at baseline and at the end of the study. Investigators also questioned patients and observed any signs or symptoms on study days 1 to 7, and at random intervals thereafter. The patients were also instructed to report any spontaneous symptoms they experienced during the study period.

**Statistical Analysis**

Results were expressed as mean (SD). Sex differences in PK properties were assessed by comparing $T_{\text{max}}$ using the Wilcoxon signed rank test, and, for the other variables, log-transformed data were compared using the independent-samples $t$ test. Achievement of a steady state was determined using 1-way analysis of variance to compare $C_{\text{min}}$ levels on days 18 to 21. Analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois). A 2-tailed $P$ value was used, and the level of statistical significance was set at $P < 0.05$.

**RESULTS**

**Patient Population**

Twelve patients participated in the study (6 men, 6 women; mean [SD] age, 26.1 [7.0] years; mean [SD] weight, 56.6 [9.0] kg; mean [SD] PANSS score, 116.8 [12.2]); 11 completed it. One patient discontinued treatment due to the onset of EPS. The characteristics of the study patients are shown in Table I.

**Pharmacokinetic Properties**

Steady state was reached in all subjects by day 21. The mean plasma aripiprazole concentrations on days 21 to 28 are shown in the figure. Other PK proper-
# Table I. Demographic and baseline clinical characteristics of the study patients.*†

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>AST, µmol/L‡</th>
<th>ALT, µmol/L§</th>
<th>Cr, µmol/L‖</th>
<th>PANSS Score§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>70</td>
<td>174</td>
<td>12</td>
<td>15</td>
<td>59</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>32</td>
<td>56</td>
<td>153</td>
<td>15</td>
<td>14</td>
<td>68</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>23</td>
<td>52</td>
<td>156</td>
<td>20</td>
<td>25</td>
<td>65</td>
<td>106</td>
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<tr>
<td>4</td>
<td>M</td>
<td>35</td>
<td>64</td>
<td>175</td>
<td>14</td>
<td>16</td>
<td>72</td>
<td>124</td>
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<tr>
<td>5</td>
<td>F</td>
<td>22</td>
<td>47</td>
<td>155</td>
<td>17</td>
<td>13</td>
<td>60</td>
<td>108</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>26</td>
<td>61</td>
<td>173</td>
<td>14</td>
<td>12</td>
<td>65</td>
<td>122</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>23</td>
<td>52</td>
<td>162</td>
<td>26</td>
<td>28</td>
<td>80</td>
<td>116</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>32</td>
<td>45</td>
<td>155</td>
<td>31</td>
<td>20</td>
<td>83</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>40</td>
<td>60</td>
<td>175</td>
<td>21</td>
<td>20</td>
<td>75</td>
<td>135</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>19</td>
<td>66</td>
<td>173</td>
<td>23</td>
<td>24</td>
<td>85</td>
<td>123</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>23</td>
<td>48</td>
<td>157</td>
<td>16</td>
<td>15</td>
<td>70</td>
<td>107</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>20</td>
<td>58</td>
<td>165</td>
<td>20</td>
<td>22</td>
<td>75</td>
<td>136</td>
</tr>
<tr>
<td>All patients, mean (SD)</td>
<td>–</td>
<td>26.1 (7.0)</td>
<td>56.6 (9.0)</td>
<td>164 (9.0)</td>
<td>19.1 (5.6)</td>
<td>18.7 (5.2)</td>
<td>71.4 (8.5)</td>
<td>116.8 (12.2)</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase; Cr = creatinine; PANSS = Positive and Negative Syndrome Scale; M = male; F = female.
*All patients were Han Chinese.
†None of the patients had comorbidities or were receiving concomitant medications.
‡Normal value,19 0 to 40 µmol/L.
§Normal value,19 0 to 37 µmol/L.
‖Normal value,19 4 to 133 µmol/L.
§Scale: <90 = mild; 90 to 119 = moderate; 120 to 150 = severe.6
Figure. Mean (SD) plasma concentrations after multiple (19 days [steady state]) oral doses of aripiprazole 10 mg q12h in Han Chinese patients with schizophrenia (N = 11).

Values are shown in Table II. After multiple oral doses (10 mg q12h), the mean (SD) t_{1/2b}, C_{SS max}, T_{max}, MRT, V/F, and CL/F were 62.2 (9.0) hours (range, 42.6-77.0 hours), 557.3 (135.5) ng/mL, 2.6 (1.1) hours (range, 1-4 hours), 84.5 (11.2) hours, 173 (48) L, and 1.9 (0.5) L/h, respectively. No significant sex differences in PK results were found (Table III).

In Han Chinese patients, the t_{1/2} values were numerically similar (62.2 [9.0] vs 68.1 [22.9] hours); C_{SS max} values were numerically higher (557.3 [135.5] vs 393 [181] ng/mL); and V/F and CL/F values were numerically lower (V/F: 173 [48] vs 196 [66] L; CL/F: 1.9 [0.5] vs 3.4 [1.6] L/h) when compared with healthy white male volunteers.12

Tolerability

All 12 patients were included in the tolerability analysis. In the study, adverse effects generally occurred early in the drug administration period and were mild to moderate. The most common adverse events were lightheadedness (5 of 12 patients), somnolence (3), tachycardia (3), hypodynamia (2), and an EPS (1). The EPS, a convulsive movement of the muscles related to the larynx, led to discontinuation. No clinically significant changes in other tolerability parameters were reported.
Table II. Steady-state pharmacokinetic properties after multiple oral doses of aripiprazole 10 mg PO q12h in Han Chinese patients with schizophrenia (N = 11). Values are mean (SD).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha), h(^{-1})</td>
<td>0.309 (0.227)</td>
<td>V/F, L</td>
<td>173 (48)</td>
</tr>
<tr>
<td>(\beta), h(^{-1})</td>
<td>0.011 (0.002)</td>
<td>CL/F, L/h</td>
<td>1.9 (0.5)</td>
</tr>
<tr>
<td>(k_{10}), h(^{-1})</td>
<td>0.024 (0.018)</td>
<td>(C_{ss, min}) ng/mL</td>
<td>388.4 (108.7)</td>
</tr>
<tr>
<td>(k_{12}), h(^{-1})</td>
<td>0.114 (0.100)</td>
<td>(C_{ss, max}) ng/mL</td>
<td>557.3 (135.5)</td>
</tr>
<tr>
<td>(k_{21}), h(^{-1})</td>
<td>0.182 (0.146)</td>
<td>(C_{ss, av}) ng/mL</td>
<td>457.7 (115.8)</td>
</tr>
<tr>
<td>(t_{1/2, k_{a}}), h</td>
<td>0.3 (0.2)</td>
<td>AUC(_{ss, 0-12}) ng/mL \cdot h(^{-1})</td>
<td>5492 (1390)</td>
</tr>
<tr>
<td>(t_{1/2, k_{e}}), h</td>
<td>4.4 (3.5)</td>
<td>AUC(_{ss, 0-192}) ng/mL \cdot h(^{-1})</td>
<td>35,171 (11,588)</td>
</tr>
<tr>
<td>(T_{\text{max}}), h</td>
<td>2.6 (1.1)</td>
<td>AUC(_{ss, 0-\infty}) ng/mL \cdot h(^{-1})</td>
<td>38,678 (12,639)</td>
</tr>
<tr>
<td>(t_{1/2, \beta}), h</td>
<td>62.2 (9.0)</td>
<td>FL, %</td>
<td>30.4 (8.2)</td>
</tr>
<tr>
<td>MRT, h</td>
<td>84.5 (11.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\alpha\) = slope of the distribution phase; \(\beta\) = slope of the elimination phase; \(k_{10}\) = elimination rate constant; \(k_{12}\) = distribution rate of drug transfer from the central compartment to the peripheral compartment; \(k_{21}\) = transfer rate constant from the peripheral compartment to the central compartment; \(t_{1/2\, k_{a}}\) = half-life of the \(k_{a}\) phase, where \(k_{a}\) is the slope of the absorption phase; \(t_{1/2\, k_{e}}\) = half-life of the \(k_{e}\) elimination phase; MRT = mean residence time; V/F = apparent volume of distribution; CL/F = oral clearance at steady state; \(C_{ss\, min}\) = \(C_{min}\) at steady state; \(C_{ss\, av}\) = mean plasma concentration over the 12-hour drug administration interval; \(AUC_{ss\, 0-12}\) = AUC from time 0 to 12 hours at steady state; \(AUC_{ss\, 0-192}\) = AUC from time 0 to 192 hours at steady state; \(AUC_{ss\, 0-\infty}\) = AUC from time 0 to infinity at steady state; FL = fluctuation percentage.

**DISCUSSION**

The recommended dosage of aripiprazole is 10 to 30 mg/d.\(^1\) The results of this study suggest that the tested dosage of aripiprazole, 10 mg q12h, was well-tolerated in these Han Chinese patients with schizophrenia. Based on previous reports of the \(t_{1/2}\) of aripiprazole,\(^1\) it might be administered once daily. For the determination of possible treatment-emergent adverse effects\(^2\) and their dose-response relationships, patients received aripiprazole 10 mg QD for 2 days at the beginning of treatment, and 10 mg q12h thereafter.

Because patients discontinued aripiprazole from days 21 to 28 for the determination of aripiprazole \(t_{1/2}\), clozapine 25 to 100 mg/d was administered as replacement treatment from observation day 25. In an in vitro study, Shin et al\(^11\) found that all antipsychotic drugs tested competitively inhibited dextromethorphan O-demethylation, a selective marker for CYP2D6, in a concentration-dependent manner. The therapeutic plasma clozapine concentration had been reported as 1.377 \(\mu\)mol/L.\(^1\) Therefore, the predicted percentage of inhibition of CYP2D6 was 3.11%. Based on that prediction, Shin et al\(^11\) hypothesized that clozapine would not significantly inhibit CYP2D6 in vivo. Clozapine was not found to notably inhibit CYP3A4. Those findings suggested that clozapine at 1.377 \(\mu\)mol/L was not associated with a PK drug interaction with aripiprazole (ie, clozapine would not interfere with the \(t_{1/2}\) determination of aripiprazole).
Table III. Steady-state pharmacokinetic properties of aripiprazole 10 mg PO q12h in female and male Han Chinese patients with schizophrenia.* Values are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Female (n = 6)</th>
<th>Male (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2 \alpha}$ h</td>
<td>0.2 (0.2)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>$t_{1/2 \beta}$ h</td>
<td>5.9 (3.8)</td>
<td>2.8 (2.5)</td>
</tr>
<tr>
<td>$t_{1/2 \gamma}$ h</td>
<td>64.8 (4.9)</td>
<td>59.2 (12.3)</td>
</tr>
<tr>
<td>MRT, h</td>
<td>86.6 (7.3)</td>
<td>82.1 (15.3)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>2.7 (1.4)</td>
<td>2.6 (0.9)</td>
</tr>
<tr>
<td>$C_{ss \text{min}}$, ng/mL</td>
<td>387.5 (100.0)</td>
<td>389.5 (133.3)</td>
</tr>
<tr>
<td>$C_{ss \text{max}}$, ng/mL</td>
<td>526.1 (131.7)</td>
<td>594.8 (144.8)</td>
</tr>
<tr>
<td>$C_{ss \text{av}}$, ng/mL</td>
<td>453.7 (106.9)</td>
<td>462.5 (138.6)</td>
</tr>
<tr>
<td>V/F, L</td>
<td>166 (56)</td>
<td>181 (52)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
</tr>
<tr>
<td>AUC$_{ss \text{0-12}}$, ng/mL·h$^{-1}$</td>
<td>5444 (1282)</td>
<td>5550 (1663)</td>
</tr>
<tr>
<td>AUC$_{ss \text{0-\infty}}$, ng/mL·h$^{-1}$</td>
<td>40,481 (13,142)</td>
<td>36,514 (13,145)</td>
</tr>
</tbody>
</table>

$t_{1/2 \alpha} = \text{half-life of the } \alpha \text{ distribution phase}; \ t_{1/2 \beta} = \text{half-life of the } \beta \text{ elimination phase}; \ MRT = \text{mean residence time}; \ T_{\text{max}} = \text{time to } C_{\text{max}} \text{ at steady state}; \ C_{\text{ss min}} = C_{\text{min}} \text{ at steady state}; \ C_{\text{ss av}} = \text{mean plasma concentration over the 12-hour drug administration interval}; \ V/F = \text{apparent volume of distribution}; \ CL/F = \text{oral clearance at steady state}; \ AUC_{ss \text{0-12}} = \text{AUC from time 0 to 12 hours at steady state}; \ AUC_{ss \text{0-\infty}} = \text{AUC from time 0 to infinity at steady state}.

*No significant between-sex differences were found.

In the present study, the PK properties of aripiprazole determined from these Han Chinese patients with schizophrenia suggest that the absorption rate of the drug was relatively rapid compared with the distribution and elimination rates. The $t_{1/2}$ obtained using this model was similar to those reported previously by Mallikaarjun et al.² but the mean $C_{ss \text{ max}}$ and $C_{ss \text{ min}}$ values were 557.3 and 388.4 ng/mL, respectively, which were higher than those previously reported and might have been associated with the lower V/F and CL/F values we found. Those differences in the PK properties of aripiprazole between Han Chinese schizophrenic patients and those in a population of healthy white male volunteers reported previously¹² might be explained by the differences in mean body mass index between these 2 populations. Another possible reason for the differences might be that all of the patients in the present study achieved steady state by day 21, whereas 20 of 6 subjects (20-mg/d group) in the literature¹² achieved plasma concentrations only within 90% of steady state by the end of the study (day 14).

**Study Limitations and Future Direction**

The results of the present study should be interpreted with caution due to the following limitations. Though this study examined both men and women, the comparison group consisted of only white males. The sample size was
small. The dose studied did not include the 10- or 30-mg/d dosages recommended by the manufacturer. We examined only this fixed dosage due to difficulty in collecting patient data. Thus, future studies should extend the dosage range of aripiprazole. They should also include investigations of metabolic profile and drug interactions of aripiprazole in Han Chinese patients with schizophrenia.

CONCLUSIONS

In this small pilot study of the PK properties of aripiprazole 10 mg PO q12h in Han Chinese patients with schizophrenia, the mean $t_{1/2}$ value was numerically similar to that previously reported in a population of healthy white male volunteers. However, the mean $C_{ss max}$ value was numerically higher, and $V/F$ and $CL/F$ values were numerically lower, compared with those in healthy white male volunteers.

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