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ORIGINAL RESEARCH ARTICLE

Bioequivalence and Pharmacokinetic Evaluation of Two Formulations of Risperidone 2 mg

An Open-Label, Single-Dose, Fasting, Randomized-Sequence, Two-Way Crossover Study in Healthy Male Chinese Volunteers

Yun Liu · Meng-qi Zhang · Jing-ying Jia · Yan-mei Liu · Gang-yi Liu · Shui-jun Li · Wei Wang · Li-ping Weng · Chen Yu

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Abstract

Background Risperidone is a benzisoxazole derivate and is effective in the treatment of schizophrenia and other psychiatric illnesses in adults and children. Although there are a few reports in the literature regarding the pharmacokinetic characteristics of risperidone, insufficient data on its pharmacokinetic properties in a Chinese population are available.

Objective To meet the requirements for marketing a new generic product, this study was designed to compare the pharmacokinetic properties and bioequivalence of two 2 mg tablet formulations of risperidone: a newly developed generic formulation (test) and a branded formulation (reference) in healthy adult male Chinese volunteers.

Methods A single-dose, open-label, randomized-sequence, 2 × 2 crossover study was conducted in fasted healthy male Chinese volunteers. Eligible participants were randomly assigned in a 1:1 ratio to receive 1 tablet (2 mg each) of the test formulation (Risperidone tablet; Dr. Reddy's Laboratories Ltd., Hyderabad, India) or the reference formulation (Risperdal® tablet; Xian-Janssen Pharmaceutical Ltd., Xi-an, China), followed by a 2-week washout period and subsequent administration of the alternate formulation. The study drugs were administered after a 10-hour overnight fast. Plasma samples were collected over 96 hours. Plasma concentrations of the parent drug, risperidone, and its active metabolite, 9-hydroxy-risperidone, were analyzed by a liquid chromatography–tandem mass spectrometry method. The formulations would be considered bioequivalent if the 90% confidence intervals (CIs) of the natural log-transformed values were within the predetermined 80–125% equivalence range for the maximum plasma drug concentration (C_{max}) and the area under the plasma concentration–time curve (AUC), in accordance with guidelines issued by the US Food and Drug Administration. Assessment of tolerability was based on recording of adverse events (AEs), monitoring of vital signs, electrocardiograms, and laboratory tests at baseline and at completion of the study.

Results A total of 24 healthy male Chinese volunteers (mean age 22.9 years [standard deviation (SD) 2.7, range 19.2–27.1]; weight 63.2 kg [SD 7.0, range 52.0–78.0]; and height 171.3 cm [SD 6.1, range 162.0–187.0]) were enrolled, and all completed the study. For the parent drug, risperidone, the 90% CIs of the relative values (test vs. reference) of the C_{max}, AUC from time zero to time t (AUC_t), and AUC from time zero to infinity (AUC_∞) were 97.0–124.0%, 92.7–115.1%, and 92.8–114.2%, respectively. For the active metabolite, 9-hydroxy-risperidone, the values were 104.4–117.7%, 101.0–113.7%, and 100.4–113.4%, respectively. The two formulations met the predetermined criteria for bioequivalence. A total of 73 AEs were observed in 24 subjects during the study. The most common AE was sedation (48 events), followed by nasal reactions (14 events), postural hypotension (3 events), hypertriglyceridemia (2 events), dizziness (4 events), nausea (1 event), and anorexia (1 event). Their severity was as follows: 16 were mild, 57 were moderate, and none were severe. The majority of the AEs were considered to be related (48 events) or probably related (23 events) to the study medication. No clinically significant abnormalities on physical examination, vital sign measurements, or electrocardiographic recordings were reported. No serious AEs were reported.

Y. Liu · M. Zhang · J. Jia · Y. Liu · G. Liu · S. Li · W. Wang · L. Weng · C. Yu (✉)
Central Laboratory, Shanghai Xuhui Central Hospital, Shanghai 200031, China
e-mail: cyu@shxh-centerlab.com

Conclusions The data from this study in healthy adult male Chinese subjects suggest that the test formulation met the regulatory criteria for bioequivalence to the reference formulation, on the basis of the rate and extent of absorption. Both formulations were well tolerated.

1 Introduction

Risperidone is a benzisoxazole derivate belonging to the class of second-generation antipsychotics. It selectively antagonizes the dopamine (D_2) and serotonin ($5\text{-}HT_2$) receptor systems in the brain and has a lower propensity than classical neuroleptics such as haloperidol to induce extrapyramidal adverse events (AEs) at therapeutic doses [1–3]. Risperidone is effective in the treatment of schizophrenia and other psychiatric illnesses in adults and children [4, 5].

Risperidone is well absorbed (94%) after oral administration, reaching the maximum plasma concentration (C_{max}) within 1–2 hours. Food does not affect the rate or the extent of absorption of risperidone. The volume of distribution is 1–2 L/kg, and the plasma protein binding of risperidone is 90% [6]. Risperidone is extensively metabolized in the liver. The main metabolic pathway is 9-hydroxylation by cytochrome P450 (CYP) 2D6, and the principal metabolite, 9-hydroxy-risperidone, has been shown to be nearly equipotent to risperidone in animal studies [7, 8]. Because CYP2D6 is subject to genetic polymorphism, the elimination half-life ($t_{½}$) of risperidone has been shown to be about 3 hours in extensive metabolizers and 20 hours in poor metabolizers, while the $t_{½}$ of 9-hydroxy-risperidone was about 21 hours in extensive metabolizers and 30 hours in poor metabolizers [7]. Risperidone and its metabolites are eliminated via the urine (70%) and, to a much lesser extent, via the feces [9].

Although several generic oral formulations of risperidone are available in China, a search of Medline and ScienceDirect (from inception to January 22, 2010), using the search terms 'risperidone', 'pharmacokinetic', 'bioavailability', and 'bioequivalence', failed to identify published data concerning the bioavailability of each formulation in a Chinese population [10, 11]. To allow marketing of a new generic risperidone tablet by regulatory authorities, the present study was designed to compare the bioequivalence of the test formulation and a reference formulation in healthy Chinese male volunteers.

2 Subjects and Methods

This study was conducted at the Phase I Clinical Center of Shanghai Xuhui Central Hospital (Shanghai, China). The study was performed in accordance with the ethical principles for studies in humans described in the Declaration of Helsinki and its amendments [12], the International Conference on Harmonisation Guideline for Good Clinical Practice [13], and the Guideline for Good Clinical Principles recommended by the State Food and Drug Administration (SFDA) of China [14]. The study protocol and the informed consent form were approved by the independent ethics committee of Shanghai Xuhui Central Hospital.

2.1 Subjects

Healthy male Chinese volunteers aged between 18 and 40 years and with a body mass index of 19–24 kg/m^2 were enrolled in the study. Eligibility for enrollment was determined by documentation of the complete medical history, a physical examination, monitoring of vital signs (including the resting blood pressure, heart rate, oral body temperature, and respiratory rate), a 12-lead electrocardiogram, and laboratory analyses (measuring the complete blood count, total bilirubin, direct bilirubin, serum creatinine, fasting blood glucose, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum albumin, sodium, potassium, calcium, hepatitis B surface antigen, hepatitis C antibody, and HIV antibodies).

Subjects were excluded from enrollment if they were active smokers, had a history of alcohol or drug abuse, and/or had any clinically significant abnormality, on the basis of their medical history, physical examination, and laboratory analyses.

The subjects were instructed to abstain from using any medications for at least 14 days prior to and during the study. The subjects were informed about the details of the study, including the risks and benefits, and provided written informed consent before study participation. They were free to withdraw from the study at any time.

2.2 Study Design and Blood Sampling

This study was a single-dose, open-label, randomized-sequence, 2 × 2 crossover bioequivalence study. The two periods were separated by a 2-week washout period based on the known $t_{½}$ values of risperidone (≤20 hours) and 9-hydroxy-risperidone (≤30 hours). The subjects were assigned to one of two sequence groups, using a random number table generated by SAS® version 9.1.3 software (SAS Institute Inc., Cary, NC, USA).

During each study period, the subjects received a single 2 mg risperidone tablet of the test formulation (Risperidone tablet [Dr. Reddy's Laboratories Ltd., Hyderabad, India]; lot # C83671; expiration date 07/2010) or a reference formulation (Risperdal® tablet [Xian-Janssen Pharmaceutical

Ltd., Xi-an, China]; lot # 080530784; expiration date 04/2011). Each treatment was administered with 240 mL of water after 10 hours of overnight fasting, and a mouth check was performed after each dosing to ensure that the subjects had ingested the study drug. Water was allowed for up to 2 hours before drug intake and from 2 hours after drug intake. A standardized lunch and dinner (8 kcal/kg body weight; 55% carbohydrate, 15% protein, and 30% fat) were provided at 4 and 9 hours after dosing, respectively. Food intake was allowed 4 hours after treatment. Alcoholic beverages, coffee, xanthine-containing drinks, intense physical activity, and smoking were not allowed during the study. Food intake was strictly controlled, and all subjects received the same food to minimize the effects of food on the study outcomes.

The subjects were under continuous medical supervision at the controlled site throughout the study. Blood samples of ~3 mL were drawn through a heparin-locked catheter (B. Braun Co., Penang, Malaysia) containing 0.5 mL of 0.4% heparin sodium. Samples were obtained before study drug administration (at baseline) and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 48, 72, and 96 hours after study drug administration. Just before each blood sample was collected, heparin in the heparin-locked catheter was discarded with 1 mL of blood, and 3 mL of blood was collected into a vacuum tube. Plasma was separated by centrifugation at 1,000 × *g* for 5 minutes at room temperature (20 °C) within 30 minutes after collection, followed by direct transfer into 2 mL polypropylene tubes and storage at −30 °C until analysis by liquid chromatography with tandem mass spectrometry (LC–MS/MS).

2.3 Tolerability Assessments

Tolerability assessments consisted of monitoring and recording of AEs, regular monitoring of clinical laboratory tests (hematology, urinalysis, and blood biochemistry), physical examinations, monitoring of vital signs, and electrocardiograms.

Physical examinations were performed before and 96 hours after drug administration. The blood pressure and pulse rate were measured at screening, before dosing, and at 0, 2, 4, 8, 12, 24, 48, 72, and 96 hours after dosing. The blood pressure and pulse rate were measured using an automatic sphygmomanometer (Omron model HEM-746C; Omron Health Care, Kyoto, Japan) after the subject had been seated quietly for ≥3 minutes, with the arm supported at heart level. Out-of-range blood pressure and pulse rate measurements were repeated at the investigator's discretion. Laboratory tests and an electrocardiogram were performed at baseline and at completion of the study. For hematology, blood was assayed using a Sysmex XT-2000^{TM} Automated Hematology Analyzer (Sysmex Corporation, Kobe, Japan). Urinalysis was performed with a CombiScan® 500 urine analyzer (Analyticon Biotechnologies AG, Lichtenfels, Germany). Blood chemistry was determined using a Siemens Advia® 2400 Chemistry Analyzer (Siemens, Erlangen, Germany). All analyses were performed at the laboratory of Shanghai Xuhui Central Hospital, which has been authorized by the local Health Authority to provide laboratory services. The laboratory is audited regularly by the National Center for Clinical Laboratories (NCCL) of China.

AEs were assessed and recorded using direct observation, spontaneous reporting, and nonspecific questioning at each study visit, without group masking, by one physician in charge at the Phase I Clinical Center of Shanghai Xuhui Central Hospital. Any undesirable sign, symptom, or medical condition occurring after the start of the study was recorded regardless of any suspected relationship to the study drug.

2.4 Determination of Plasma Concentrations of Risperidone and the Active Moiety, 9-Hydroxy-Risperidone

Plasma concentrations of the parent drug, risperidone, and its active metabolite, 9-hydroxy-risperidone, were determined by the Central Laboratory of Shanghai Xuhui Central Hospital, using a validated LC–MS/MS method, in accordance with US Food and Drug Administration (FDA) guidelines for bioanalytic method validation [15, 16]. Technicians were blinded to the treatment groups as the assays were completed. Plasma samples were extracted using a liquid–liquid extraction technique. Five microliters of mixed internal standard (d4-risperidone and d4-9-hydroxy-risperidone, both 50 ng/mL) spiking solution was added to 50 µL of the plasma sample, then 0.6 mL of tert-butyl methyl ether was added into the polypropylene centrifuge tube and the tube was shaken on a vortex for 5 minutes. Subsequently, the mixture was centrifuged for 3 minutes at 23,755 × *g* (Hettich Mikro 22R, Andreas Hettich GmbH & Co KG, Tuttlingen, Germany). The upper ethereal layer was decanted into another tube, where it was evaporated to complete dryness under a nitrogen stream at 45 °C. Samples were reconstituted with 100 µL of methanol–water (30:70, v/v) and a 10 µL sample was then injected into the LC–MS/MS system. A similar sample extraction method has been described elsewhere, using 0.2 mL (Cabovska et al.) [16] or 0.5 mL (Zhang et al.) [17], but in our method we used a lower sample volume and methanol–water as the reconstitute solution instead of ammonium acetate solution [16].

The liquid chromatographic system (Shimadzu Corporation, Kyoto, Japan) was equipped with two LC-20ADvp pumps, a DGU-20A_3 vacuum degasser, an SIL-HT$_C$ autosampler, and a controller module. Chromatographic

separation was achieved on a 100 × 2.0 mm, 5 μm Capcell PAK C_{18} MGIII column (Shiseido Co. Ltd., Tokyo, Japan) protected with a 4.0 × 3.0 mm, 5 μm C_{18} guard cartridge (Phenomenex Inc., Torrance, CA, USA). The mobile phase consisted of 5 mM ammonium acetate solution/acetonitrile (50:50, v/v) at a flow rate of 0.4 mL/min. The samples were kept at 4 °C in an autosampler, and a volume of 10 μL was injected for analysis.

Mass spectrometric detection was performed on a 3200 QTrap® instrument (ABI-Sciex, Toronto, ON, Canada) equipped with a turbo spray interface and operated in positive ionization mode. The dwell time was set at 200 ms, and the ion source temperature was set at 450 °C, with ultra-high-purity nitrogen as the curtain gas (20) and collision gas (medium). The ion spray voltage was set at 1,900 V. Multiple reaction monitoring transitions were at mass-to-charge ratios (m/z) of 411.3 → 191.3 and 415.3 → 195.3 for risperidone and d4-risperidone, respectively, and 427.2 → 207.2 and 431.2 → 211.2 for 9-hydroxy-risperidone and d4-9-hydroxy-risperidone, respectively. Data acquisition and processing were powered by the Analyst® 1.4.2 software package (Applied Biosystems, Foster City, CA, USA).

The methods were linear from 0.1 to 50 ng/mL for both risperidone and the active metabolite, 9-hydroxy-risperidone. The lower limit of quantification was established at 0.1 ng/mL for both analytes. Quality control samples (0.1, 0.25, 25, 40 ng/mL) for both analytes within the calibration range were routinely analyzed with study samples. Intra-day assay validation indicated precision of 0.8–9.4% and accuracy of 92.8–104.0% for the quality control samples of risperidone, and the inter-day precision ranged from 1.5% to 7.6%, with accuracy of 97.2–104.0%. For 9-hydroxy-risperidone, the intra-day precision ranged from 1.1% to 9.1%, with accuracy of 93.8–103.8%, and the inter-day precision ranged from 1.4% to 6.1%, with accuracy of 96.9–100.8%. Both risperidone and 9-hydroxy-risperidone were stable in human plasma following three freeze–thaw cycles, for 24 hours at room temperature, for up to 4 weeks following storage at −30 °C, and for 24 hours after being processed. The coefficients of variation for stability tests were all within 20%, which met the acceptance criteria of our laboratory's standard operating procedure. The stability tests that were performed indicated that there was no significant degradation under the conditions that were described.

2.5 Pharmacokinetic and Statistical Analysis

Pharmacokinetic analysis was conducted with a noncompartmental method, using Drug and Statistics (DAS) software version 2.0 (University of Science and Technology, Hefie, China). The C_{max} and the time to reach the C_{max} (t_{max}) were obtained directly from the concentration–time curves. Pharmacokinetic properties were analyzed by noncompartmental pharmacokinetic data analysis using PKCalc software (1986 release), based on an equation described by Shumaker [18]. The area under the plasma concentration–time curve (AUC) from time zero to time t (AUC_t) was calculated according to the linear trapezoidal rule. The AUC from time zero to infinity (AUC_∞) was calculated as $AUC_t + C_t/\lambda_z$, where C_t was the last measured concentration and λ_z was the slope of the linear regression of the natural log-transformed concentration–time curve. The $t_{½}$ was calculated as $0.693/\lambda z$ [19]. The total clearance after oral administration (CL/F) was calculated as dose/AUC_∞.

Descriptive statistics, including mean values and standard deviations (SDs), were used to summarize the pharmacokinetic data for the two drugs. Statistical analyses were performed using SAS version 9.0.2 software (SAS Institute Inc., Cary, NC, USA). An analysis of variance (ANOVA) was performed on the natural logarithm (ln)-transformed pharmacokinetic parameters (the AUC_t, AUC_∞, and C_{max}), using the general linear models procedures in SAS. The ANOVA model had fixed factors for sequence, treatment, period, and subject within sequence. The Wilcoxon signed-rank test was used for nonparametric analysis to determine differences in the t_{max}. If the 90% confidence intervals (CIs) of the AUC and C_{max} were located within 80–125% of the statistical interval proposed by the FDA [20], the two drugs would be considered bioequivalent.

On the basis of the variability reported in a previous trial in India and the Chinese SFDA guidance [19], the number of subjects required to demonstrate bioequivalence at a significance level of 5% with 90% power was calculated to be 24.

3 Results

3.1 Demographic Data

A total of 24 healthy male Chinese volunteers were enrolled, and all completed the study. The demographic characteristics of the study population are summarized in Table 1.

3.2 Tolerability

The tolerability of the two formulations of risperidone, each given in a single administration, was acceptable. No serious AEs occurred during treatment with the test formulation or the reference formulation. A total of 73 AEs were observed in 24 subjects during the study, and the

Table 1 Baseline demographic and clinical characteristics of the study population (n = 24 healthy Chinese male volunteers)

Characteristic	Value
Age (years)	
Mean [SD]	22.9 [2.7]
Range	19.2–27.1
Weight (kg)	
Mean [SD]	63.2 [7.0]
Range	52.0–78.0
Height (cm)	
Mean [SD]	171.3 [6.1]
Range	162.0–187.0
Body mass index (kg/m^2)	
Mean [SD]	21.5 [1.3]
Range	19.3–23.7

SD standard deviation

event rate was similar with both formulations (37 AEs occurred after intake of the test formulation, while 36 AEs occurred after intake of the reference formulation). The most common AE was sedation (48 events), followed by nasal reactions (14 events), postural hypotension (3 events), hypertriglyceridemia (2 events), dizziness (4 events), nausea (1 events), and anorexia (1 events). Their severity was as follows: 16 were mild, 57 were moderate, and none were severe. The majority of the AEs were considered to be related (48 events) or probably related (23 events) to the study medication. No clinically significant abnormalities on physical examination, vital sign measurements, or electrocardiographic recordings were reported.

3.3 Pharmacokinetic Analysis

The mean plasma concentration–time curves of the parent drug, risperidone, and its active metabolite, 9-hydroxy-risperidone, after administration of an oral dose of single 2 mg tablets of two formulations to the 24 Chinese healthy male subjects are shown in Fig. 1. The primary pharmacokinetic parameters of the parent and metabolite are listed in Table 2. The mean C_{max} values of the parent and metabolite after administration of the test tablets (15.84 [SD 7.48] and 11.69 [SD 5.15] ng/mL, respectively) were similar to those after administration of the reference tablets (14.66 [SD 6.97] and 11.25 [SD 5.14] ng/mL, respectively). The mean t_{max} values of the parent and metabolite were 1.02 [SD 0.97] and 6.24 [SD 5.06] hours, respectively, for the test formulation, and 1.09 [SD 1.14] and 5.79 [SD 3.61] hours, respectively, for the reference formulation. The results for the extent of absorption, as determined by the mean AUC_t and AUC_∞ values, were 96.84 [SD 79.73] and 97.89 [SD 79.72] ng·h/mL, respectively, for the

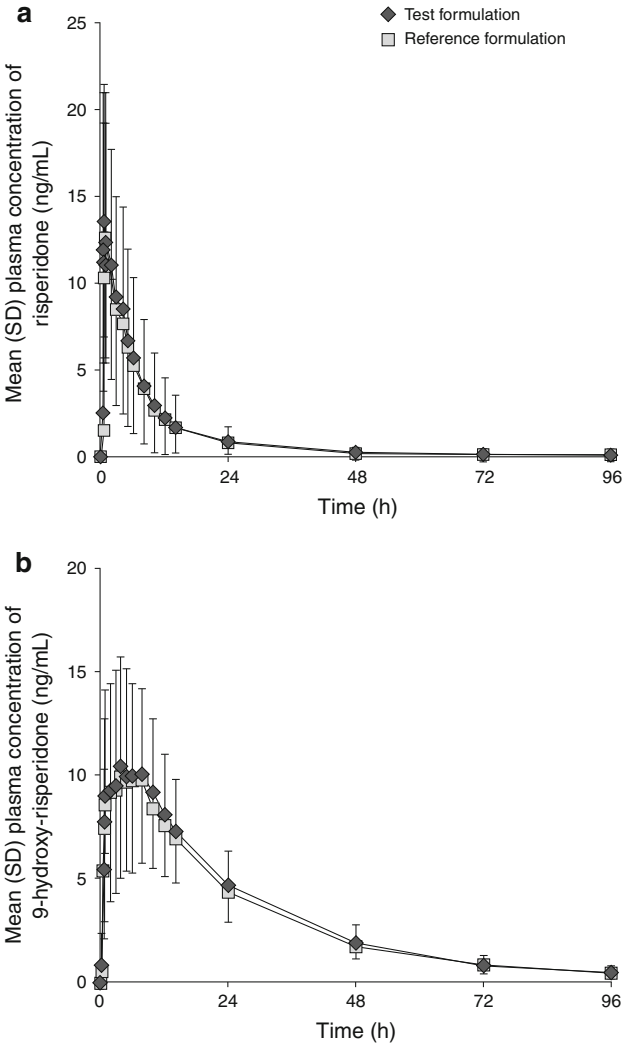

Fig. 1 Mean [standard deviation] plasma concentration–time profiles of (**a**) risperidone and (**b**) 9-hydroxy-risperidone after administration of a single 2 mg dose of the test formulation (Risperidone tablet; Dr. Reddy's Laboratories Ltd., Hyderabad, India) and the reference formulation (Risperdal® tablet; Xian-Janssen Pharmaceutical Ltd., Xi-an, China) to 24 healthy Chinese male volunteers

parent, and 317.67 [SD 96.99] and 332.55 [SD 101.93] ng·h/mL, respectively, for the metabolite after administration of the test formulation, and 89.88 [SD 69.24] and 91.35 [SD 69.51] ng·h/mL, respectively, for the parent, and 301.86 [SD 96.87] and 316.11 [SD 101.19] ng·h/mL, respectively, for the metabolite after administration of the reference formulation. The mean $t_{½}$ values of 9-hydroxy-risperidone after intake of the test tablets and reference tablets (21.08 [SD 4.35] and 21.91 [SD 4.49] hours, respectively) appeared to be longer than those of the parent, risperidone (4.74 [SD 3.13] and 4.94 [SD 2.98] hours, respectively). When the pharmacokinetic parameters were corrected for weight, the results were not substantially different.

Table 2 Pharmacokinetic parameters of the parent drug, risperidone, and its active metabolite, 9-hydroxy-risperidone, after a single 2 mg oral dose of two formulations of risperidone tablets in healthy male Chinese volunteers (n = 24)

Parameter	Risperidone[a]		9-Hydroxy-risperidone[a]	
	Test[b]	Reference[c]	Test[b]	Reference[c]
C_{max} (ng/mL)	15.84 [7.48]	14.66 [6.97]	11.69 [5.15]	11.25 [5.14]
t_{max} (h)	1.02 [0.97]	1.09 [1.14]	6.24 [5.06]	5.79 [3.61]
AUC_t (ng·h/mL)	96.84 [79.73]	89.88 [69.24]	317.67 [96.99]	301.86 [96.87]
AUC_∞ (ng·h/mL)	97.89 [79.72]	91.35 [69.51]	332.55 [101.93]	316.11 [101.19]
$t_{½}$ (h)	4.74 [3.13]	4.94 [2.98]	21.08 [4.35]	21.91 [4.49]

AUC area under the plasma concentration–time curve, AUC_t AUC from time zero to time t, AUC_∞ AUC from time zero to infinity, C_{max} maximum plasma drug concentration, $t_{½}$ elimination half-life, t_{max} time to reach the C_{max}

[a] The data are expressed as mean [standard deviation]

[b] Risperidone tablet (Dr. Reddy's Laboratories Ltd., Hyderabad, India)

[c] Risperdal® tablet (Xian-Janssen Pharmaceutical Ltd., Xi-an, China)

On ANOVA, using logarithmic-transformed data, no significant sequence effects, treatment effects, or period effects were observed for any pharmacokinetic property of risperidone or its active metabolite, 9-hydroxy-risperidone.

The 90% CIs of the relative values (test vs. reference) of the ln-transformed C_{max}, AUC_t, and AUC_∞ values are shown in Table 3. For the parent drug, risperidone, these values were 97.0–124.0%, 92.7–115.1%, and 92.8–114.2%, respectively. For the active metabolite, 9-hydroxy-risperidone, these values were 104.4–117.7%, 101.0–113.7%, and 100.4–113.4%, respectively. The two formulations met the predetermined criteria for bioequivalence. In the nonparametric analysis, differences between the formulations did not reach the level of statistical significance in the Wilcoxon signed-rank test with regard to the t_{max} values for the two compounds.

4 Discussion

This study examined the pharmacokinetic properties and bioequivalence of two formulations of risperidone tablets in healthy adult male Chinese subjects. As shown in Fig. 1, we found nearly overlapping concentration–time curves for the two risperidone formulations. Moreover, the mean AUC_∞ and C_{max} values were not significantly different, and the 90% CIs of both the parent drug, risperidone, and the active metabolite, 9-hydroxy-risperidone, were completely contained within the predefined bioequivalence criteria of 80–125% for the primary endpoints of the AUC and C_{max} [20].

There are few reports in the literature regarding the pharmacokinetics of risperidone, and the existing reports appear to differ [10, 11]. In a single-site, open-label, randomized, two-way crossover study, a 2 mg tablet of risperidone administered to 30 healthy volunteers of both sexes produced mean values of 12.04 ng/mL and 76.09 ng·h/mL for the C_{max} and AUC_∞, respectively, of risperidone, and 11.02 ng/mL and 246.02 ng·h/mL for the C_{max} and AUC_∞, respectively, of 9-hydroxy-risperidone [11]. In the present study, the C_{max} values (15.78 and 11.69 ng/mL for risperidone and 9-hydroxy-risperidone, respectively) and the AUC_∞ values (97.89 and 332.55 ng·h/mL for risperidone and 9-hydroxy-risperidone, respectively) were both higher than those reported by Cánovas et al. [11] In another randomized, open-label, two-way crossover study by van Schaick et al. [10], 37 healthy volunteers of both sexes were administered a single dose of two 0.5 mg tablets of risperidone, with the last sample collection point being 96 hours after administration. For the parent drug, risperidone, the reported C_{max} was 9.3 ng/mL (18.6 ng/mL as normalized to a 2 mg dose), the t_{max} was 1.2 hours, and the $t_{½}$ was 3.6 hours. In our study, the C_{max} (14.66 ng/mL), t_{max} (1.09 hours), and $t_{½}$ (4.94 hours) of risperidone were all numerically lower than those reported by Schaick et al.

Although the differences between the values reported in the present study and those reported in the aforementioned studies may represent a race effect, the previously reported studies did not specify the races of their subjects. On the other hand, pharmacogenetic variables may also be involved. As mentioned previously, CYP2D6 is the major enzyme responsible for the metabolism of risperidone [8]. Thus, genetic polymorphism or other gene variations may have influenced the pharmacokinetics and bioavailability of risperidone in our population.

In accordance with the FDA guidelines [20], our study was designed to administer a single dose of each formulation, with a 2-week washout period between the two treatments. The individual $t_{½}$ values of the parent drug, risperidone, and the active metabolite, 9-hydroxy-risperidone, ranged from 1.97 to 12.59 hours and from 15.98 to

Table 3 Comparison of the 90% confidence intervals of natural log-transformed pharmacokinetic parameters of the parent drug, risperidone, and its active metabolite, 9-hydroxy-risperidone, following administration of two formulations (test[a]/reference[b]) of risperidone tablets in healthy male Chinese volunteers (n = 24)

Compound and parameter	Relative value [test[a] vs. reference[b]] (%)	90% CI (%)	*p* values	
			<80%	>125%
Risperidone				
ln C_{max}	111.0	97.0–124.0	0.00001	0.00001
ln AUC_t	103.3	92.7–115.1	0.00002	0.003
ln AUC_∞	102.9	92.8–114.2	0.00002	0.002
9-hydroxy-risperidone				
ln C_{max}	109.8	104.4–117.7	0.00001	0.00002
ln AUC_t	107.1	101.0–113.7	0.00001	0.00003
ln AUC_∞	106.7	100.4–113.4	0.00002	0.00001

AUC area under the plasma concentration–time curve, AUC_t AUC from time zero to time t, AUC_∞ AUC from time zero to infinity, *CI* confidence interval, C_{max} maximum plasma drug concentration, *ln* natural log-transformed

[a] Risperidone tablet (Dr. Reddy's Laboratories Ltd., Hyderabad, India)

[b] Risperdal® tablet (Xian-Janssen Pharmaceutical Ltd., Xi-an, China)

33.62 hours, respectively, so the 2-week washout period was sufficient to clear the residual compound from the previous period, which represents undetectable plasma concentrations at baseline of the second period in all subjects.

All AEs that occurred were expected events in healthy subjects [9]. There were no significant differences in the incidence of AEs between the test and the reference formulations, and there were no serious AEs with either formulation.

Like any clinical trial, the current study had several limitations that should be considered. Because the data were obtained only from healthy men who were administered a single dose, and the participants were studied only in the fasted state, the pharmacokinetic characteristic of risperidone might differ in target populations. These formulations are yet to be tested in patients with schizophrenia and other psychiatric illnesses. A larger study including subjects in the fed state is also necessary. Because CYP2D6 is the major enzyme involved in risperidone metabolism, some further study should be performed to determine whether CYP2D6 metabolizer status was responsible for the difference noted in the pharmacokinetic profiles of populations similar to our study sample.

5 Conclusions

The data from this study in healthy adult male Chinese subjects suggests that the test formulation met the regulatory criteria for bioequivalence to the reference formulation, on the basis of the rate and extent of absorption. Both formulations were well tolerated.

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