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Multiple dose pharmacokinetics of risperidone and 9-hydroxyrisperidone in Chinese female patients with schizophrenia

Zhi-ling ZHOU[2], Xin LI[3], Huai-yan PENG[4], Xi-yong YU[2], Ming YANG[2], Feng-li SU[1], Feng WANG[1], Rong-hua ZHU[1], Chun-yu DENG[2], Qiu-xiong LIN[2], Chuan-yue WANG[5], Wen-biao LI[5], Shu-guang LIN[2], Huan-de LI[1,6]

[1]Clinical Pharmacy Research Institute, Xiangya Second Hospital, Central South University, Changsha 410011, China; [2]Research Center of Medical Science, Guangdong Provincial People's Hospital, Guangzhou 510080, China; [3]Vascular Surgery Department, Xiangya Second Hospital, Central South University, Changsha 410011, China; [4]Department of Clinical Laboratory, Third Xiangya Hospital, Central South University, Changsha 410013, China; [5]Affiliated Beijing An Ding Hospital, Capital University of Medical Science, Beijing 100088, China

Key words

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[6] Correspondence to Prof Huan-de LI.
Phn 86-731-443-6720.
E-mail chowzl@yahoo.com.cn

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Abstract

Aim: To study the multiple dose clinical pharmacokinetics of risperidone and its main active metabolite, 9-hydroxyrisperidone, in Chinese female patients with schizophrenia. **Methods:** The subjects were 23 Chinese female inpatients aged 18–65 years who met the CCMD-III (third revision of the Chinese Criteria of Mental Disorders) criteria for schizophrenia. Subjects were tested after 17 d of treatment with 2 mg risperidone twice daily. Plasma concentrations of risperidone and 9-hydroxy-risperidone were assayed by using validated high performance liquid chromatography-mass spectrometry (HPLC-MS) methods. **Results:** Risperidone was rapidly absorbed (T_{max} was 1.6 h) and its $T_{1/2}$ in plasma was short (3.2 h). 9-hydroxy-risperidone was quickly metabolized from the parent drug with a mean T_{max} of 2.5 h. It had a long half-life of 24.7 h. The C^{ss}_{av} of risperidone and 9-hydroxy-risperidone were 36.9±33.1 and 110.6±30.5 μg·h·L^{-1}, respectively, and the AUC^{ss}_{0-12} were 443.2±397.4 and 1327.2±402.3 μg·h·L^{-1}, respectively. *CL/F* and *V/F* of risperidone were 8.7±6.2 L/h and 34.1±24.3 L, respectively. Interindividual variations for pharmacokinetic parameters were quite large for risperidone. All 23 subjects experienced high prolactin levels when treated with risperidone. However there was no correlation between prolactin level and the concentration of risperidone, 9-hydroxy-risperidone, or the active moiety. **Conclusion:** Risperidone showed large interindividual variations in pharmacokinetics. Administration of risperidone resulted in high serum prolactin levels. The results indicate that systemic exposure to risperidone and 9-hydroxy-risperidone in female Chinese schizophrenic patients is higher relative to published data for white Caucasian patients. Larger studies regarding the PK/PD relationship may be required to develop a reasonable clinical dosage regimen for Chinese female patients.

Introduction

Risperidone (RIS; Figure 1), a benzisoxazole derivative, is a relatively new antipsychotic agent that combines serotonin type 2 ($5HT_2$) and dopamine type 2 (D_2) receptor antagonism[1]. RIS has been shown to be an effective antipsychotic, affecting both the positive and negative symptoms of schizophrenia, with a low incidence of extrapyramidal symptoms (EPS) and a lack of anticholinergic effects[2–3]. When administered orally to healthy volunteers, RIS was absorbed rapidly, achieved a peak plasma concentration within 2.14 h[4], and displayed linear pharmacokinetics at doses between 0.5 mg and 25 mg[5]. RIS is extensively metabolized in the liver by CYP2D6 to a major metabolite, 9-hydroxyrisperidone (9-OH-RIS; Figure 1)[6–7], which is eliminated by renal excretion[8], and CYP3A4 also catalyzes the

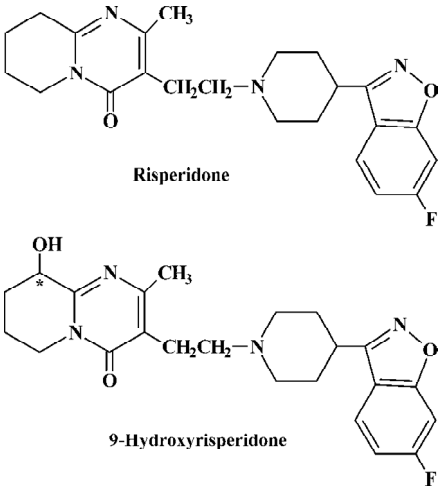

Figure 1. Chemical structures of risperidone and 9-hydroxyrisperidone.

formation of (-)-9-hydroxyrisperidone *in vitro*[9–10]. Studies in animals[8] and receptor binding *in vitro*[8] and *in vivo*[11] indicate that 9-OH-RIS has approximately 70% of the pharmacological activity of RIS. Therefore, the total active risperidone moiety (RIS plus 9-OH-RIS) is considered to be the most clinically relevant measure[12]. Although RIS has a half-life of 2–4 h in CYP2D6 extensive metabolizers and up to 20 h in poor metabolizers, the pharmacokinetic profile of the active moiety after single and multiple doses was similar in extensive and poor metabolizers, with an overall mean elimination half-life of 20 h[6,12–14].

Risperidone has been widely used to treat schizophrenia or schizophreniform disorders after it was put on the market in 1993 in China. However, the steady-state pharmacokinetics of RIS in Chinese patients, especially Chinese female patients, who, relative to Chinese male patients, have a higher prevalence of schizophrenia[15–20], higher serum levels of prolactin after administration of RIS[21], receive less family concern, and have lower educational levels[22,23], has not previously been systematically studied. The aim of the present study was to determine the pharmacokinetics of repeated oral doses and to document the safety of RIS in Chinese female patients suffering from schizophrenia or schizophreniform diseases.

Materials and methods

Drugs and reagents RIS (purity 99%) and 9-OH-RIS (purity 99%) standards were donated by Xi'an Janssen Pharmaceutical (Xi'an, Shanxi, China). Quetiapine (IS; purity >99.6%) was kindly provided by Hunan Dongting Pharmaceutical (Changde, Hunan, China). RIS tablets (batch no: AM 010910767, 1 mg/tablet) were kindly donated by Xi'an Janssen Pharmaceutical. High performance liquid chromatography (HPLC) grade reagents (methanol, acetonitrile and ammonium acetate) were purchased from Tedia (Fairfield, OH, USA). Other AR grade reagents were purchased from the Chemical Reagents Factory of Hunan province (Changsha, Hunan, China).

Apparatus Waters 2690 HPLC equipment system, micromass ZQ mass spectrometer (Wythenshawe, Manchester, UK) equipped with an electrospray ionization (ESI) ion source, Compaq Deskpro Workstation, and Masslynx 3.5 software were used.

Study subjects Chinese female in-patients aged 18–65 years were recruited to the study. All the subjects were diagnosed with schizophrenia or schizophreniform disorders according to the Chinese Criteria of Mental Disorders (CCMD, 3rd edition), completed during 1996–2000 by 114 renowned Chinese psychiatrists with reference to ICD-10 from WHO and DSM-IV from American. On the basis of their medical history, a physical examination and routine laboratory tests, no patients had hepatic, renal, cardiac, hematological or other diseases. Cigarettes and alcohol were restrained. Patients who were also being treated with drugs known to inhibit or induce the activity of CYP2D6 or CYP3A4 were excluded. Written informed consent was obtained from each parent or patients' legal guardian. The Ethical Committee of Xiangya Second Hospital of Central South University approved the protocol.

Experimental protocol The present study was an open label and single-center trial. All the subjects were treated using a titration scheme. The titration scheme comprised 0.5 mg doses of RIS twice daily (bid) for 2 d, 1 mg bid for 5 d, 2 mg bid for 7 d, followed by 2 mg qd for 1 d. On d 15, following an overnight fast, a final dose of RIS was administered in the morning and serial blood samples (2–3 mL) were collected before the final dose and at 0.5, 1.25, 2, 3, 4, 6, 8, 12, 24, and 48 h after the final dose. To confirm the steady-state concentrations of RIS and 9-OH-RIS, blood samples for trough plasma concentrations were collected before the morning dose of RIS on d 13 and 14. Plasma was separated by centrifugation and stored at -80 ºC. During the trial, all subjects had the same diet.

Safety assessments Adverse events (AE) were monitored throughout the trial, together with an assessment of their severity and possible relationship to the administration of RIS. A complete physical examination was performed at screening and at the end of the study. Vital signs, including blood pressure and pulse rate, were measured at screening,

d 0 and 16, and at the end of the study. A standardized 12-lead electrocardiogram (ECG) was performed at screening and on d 0 and 16. Clinical laboratory tests, including hematology and clinical chemistry, were performed at screening and on d 0 and 16. Serum prolactin concentration was determined at 7:00 AM on d 0 and 16, and at the end of the study.

Analytical methods Plasma concentrations of RIS and 9-OH-RIS were determined using a validated procedure described elsewhere[24,25], involving liquid-liquid extraction of RIS and 9-OH-RIS and detection by high-performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS). Calibration curves were linear over the concentration range of 0.5 to 200 μg/L for RIS and 5 to 250 μg/L for 9-hydroxyrisperidone. The correlation coefficient obtained by linear regression were 0.9905 for RIS, and 0.9926 for 9-OH-RIS. The limit of quantification was 0.5 μg/L for RIS and 5 μg/L for 9-OH-RIS. Recovery of RIS and 9-OH-RIS was examined at 3 different concentrations. The recovery rates were greater than 80.3% for RIS, and greater than 78.4% for 9-OH-RIS. Intra- and interassay variability was examined at 3 concentrations for RIS and 9-OH-RIS. The intra-assay variabilities, expressed as coefficients of variation (n=5) were less than 8.1% for RIS, and less than 10.1% for 9-OH-RIS. The interassay variabilities were less than 12.8% for RIS and less than 14.2% for 9-OH-RIS.

Pharmacokinetic analysis The steady-state peak concentration (C^{ss}_{max}) and the time to the peak concentration (T_{max}) were recorded as observed. The terminal elimination rate constant (K_e) was determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. The terminal-phase elimination half-life ($T_{1/2}$) was calculated as $0.693/K_e$. AUC^{ss}_{0-12} was calculated by using the linear trapezoidal rule. The apparent volume of clearance (CL/F) and distribution (V/F) of RIS were calculated as dose/AUC^{ss}_{0-12} and CL/K_e, respectively. The steady-state trough plasma concentration (C^{ss}_{mix}) was represented by the plasma concentration collected before RIS administration on d 18. The steady-state average plasma concentration for the 0–12 h dosing interval (C^{ss}_{av}) was calculated as $AUC^{ss}_{0-12}/12$. The pharmacokinetic parameters of the active moiety (RIS plus 9-OH-RIS) were also calculated.

Statistical analysis All values are expressed as mean±SE (range). All statistical tests were 2-tailed and significance was set at the 0.05 level. Differences in the mean values of physical examinations and clinical laboratory tests before and after the study were compared by using a paired t-test.

Results

Forty subjects were originally enrolled, but 17 of these were excluded because they were outpatients or were comedicated with drugs that might have interfered with the pharmacokinetics of the study drugs or interpretation of the results. The most frequent comedications were benzodiazepines, antiparkinsonian drugs, antiepileptics, analgesics, and cardiovascular drugs. A total of 23 subjects (age 28.3±9.1; BMI 23.0±3.1) completed the present pharmacokinetics study for RIS. All the subjects were identified as extensive or medium metabolizers of CYP2D6 by phenotyping (dextromethmorphan was used as the probe drug).

The trough plasma concentrations of RIS and its metabolite, 9-OH-RIS, on d 13, 14, and 15 were not significantly different (P>0.05), indicating that steady-state concentrations of RIS and its metabolite were achieved.

The mean pharmacokinetic parameters of RIS, 9-OH-RIS, and the active moiety (RIS plus 9-OH-RIS) are summarized in Table 1. Mean steady-state plasma concentration-time curves are shown in Figure 2. After oral administration, RIS was rapidly absorbed with a mean T_{max} of 1.6 h and 9-OH-RIS was quickly metabolized from the parent drug with a mean T_{max} of 2.5 h. Pharmacokinetic studies indicated that RIS had a mean half-life of 3.2 h, a small volume of distribution (approximately 34.1 L), and a low clearance (approximately 8.7 L/h); 9-OH-RIS had a long mean half-life of 24.7 h.

We found that the pharmacokinetics parameters of RIS varied greatly among individuals. Among the 23 patients, there were 4 patients (approximately 17%) whose C^{ss}_{max} of RIS was below the limit of detection (0.5 μg/L). The coefficients of variation (CV) of V/F and CL/F were all 71% for RIS. The CV of C^{ss}_{mix} was 105% for RIS. AUC^{ss}_{0-12} also had a large CV, and the CV of RIS was 90%. For $T_{1/2}$, the CV of RIS was 40%. Compared with that of RIS, the pharmacokinetic parameters of 9-OH-RIS had lower CV values (C^{ss}_{mix} 37%; AUC^{ss}_{0-12} 30%; $T_{1/2}$ 32%). For the active moiety, the CV values of C^{ss}_{mix}, AUC^{ss}_{0-12}, and $T_{1/2}$ were 40%, 38%, and 32%, respectively.

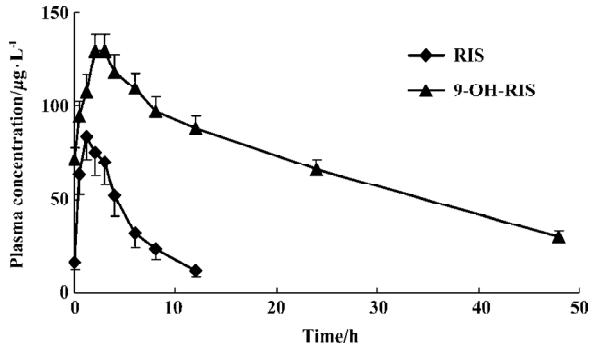

Figure 2. Mean steady-state plasma concentration-time curves of RIS and 9-OH-RIS. n=23. Mean±SEM.

Table 1. Main multiple dose pharmacokinetic parameters of RIS and 9-OH-RIS. n=23. Data are mean±SE (range).

Parameter	RIS	9-OH-RIS	Active moiety
T_{max} (h)	1.6±0.2 (0.5-4.0)	2.5±0.2 (1.25-6.0)	1.8±0.1 (1.25-3.0)
$T_{1/2}$ (h)	3.2±0.3 (1.3-6.0)	24.7±1.7 (12.5-41.2)	22.6±1.5 (12.3-40.5)
K_e (h^{-1})	0.253±0.022 (0.115-0.536)	0.030±0.002 (0.011-0.055)	0.034±0.002 (0.017-0.056)
C^{ss}_{max} ($\mu g \cdot L^{-1}$)	89.1±12.1 (34.2-217.8)	137.8±9.5 (65.4-247.4)	226.9±16.4 (113.3-438.3)
C^{ss}_{mix} ($\mu g \cdot L^{-1}$)	[1)]17.2±4.2 (0.79-58.7)	74.6±5.8 (36.6-148.7)	91.8±7.6 (41.0-197.7)
C^{ss}_{av} ($\mu g \cdot L^{-1}$)	36.9±6.9 (7.3-112.5)	10.6±7.0 (63.4-190.7)	147.5±11.7 (82.9-281.5)
AUC^{ss}_{0-12} ($\mu g \cdot h \cdot L^{-1}$)	443.2±82.9 (87.7-1349.4)	1327.2±83.9 (760.8-2288.4)	1770.4±140.3 (995.0-3378.0)
V/F (L)	34.1±5.1 (7.4-115.2)		
CL/F ($L \cdot h^{-1}$)	8.7±1.3 (1.5-22.8)		

[1)] n=19. AUC^{ss}_{0-12}, area under the concentration-time curve during an administration interval (12 h) at steady state; K_e, terminal elimination rate constant; C^{ss}_{av}, average steady-state drug concentration in plasma, blood or other body fluids during multiple administration; C^{ss}_{mix}, minimum steady-state drug concentration in plasma, blood or other body fluids during multiple administration; Tmax, time to reach peak or maximum concentration following drug administration at steady state; $T_{1/2}$, elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve; CL/F, apparent total body clearance of drug from plasma; C^{ss}_{max}, maximum steady-state drug concentration in plasma, blood or other body fluids during multiple administration; V/F, apparent volume of distribution.

Table 2 summarizes the overall incidence of AE according to the preferred terms. No deaths or serious side effects were reported during the study. No subject developed extrapyramidal side effects following the administration of RIS. No clinically significant abnormal physical examination findings, ECG results, laboratory values or vital signs was observed during the study. However, serum prolactin changed significantly (P<0.05), increasing from 14.1±7.6 μg/L before RIS was administered, to 87.2±35.7 μg/L after administration of RIS. There was no correlation between serum prolactin concentration and the concentration of RIS, 9-OH-RIS, or the active moiety. Twenty-three patients experienced a total of 35 AE, of which the majority were rated mild in intensity. In patients receiving RIS, 30 of 35 AE were considered possibly or probably related to the administration of RIS.

Table 2. Total incidence of adverse events. n=23.

Preferred term	Subjects experiencing AE (n)
Subjects with ≥ AE	22
Asthenia	1
Anxiety	3
Tachycardia	2
Dry mouth	6
Dyspepsia	1
Constipation	2
Nausea	1
Diarrhea	3
Abnormal dreams	1
Pain	1
Myalgia	1
Insomnia	3
Somnolence	3
Headache	3
Galactorrhea	4

Discussion

When compared with data obtained in a population of white people with schizophrenia[26], our data show that Chinese female patients suffering from schizophrenia have higher steady-state trough plasma concentrations (C^{ss}_{mix}) of RIS and 9-OH-RIS. In our study the of RIS and 9-OH-RIS were 19.3 and 79.5 μg/L, respectively; however, the corresponding values were found to be 2.9 and 24.1 μg/L, respectively, in the previous study[26]. A similar study also indicated that plasma levels of the antipsychotic and its metabolite are at least 2–3 times higher in Chinese female subjects than in their Western counterparts[27]. After dose-adjusting the of RIS and 9-OH-RIS in our study (RIS 221.6±198.7 $\mu g \cdot h \cdot L^{-1}$; 9-OH-RIS 663.6±201.2 $\mu g \cdot h \cdot L^{-1}$), which were much higher than corresponding values found in two previous studies (RIS 41.6±23.4 $\mu g \cdot h \cdot L^{-1}$; 9-OH-RIS 193.4±76.5 $\mu g \cdot h \cdot L^{-1}$[28])(RIS 59.6±16.3 $\mu g \cdot h \cdot L^{-1}$; 9-OH-RIS 162.1±19.2 $\mu g \cdot h \cdot L^{-1}$[29]). Some well-known inter-ethnic differences in drug metabolism deserve to be considered. There are some ethnic characteristics that might have contributed to this finding: for example the activity of the metabolic enzymes (CYP2D6 or CYP3A4), body weight, and lean body mass. Additional investigations are needed to explain this observation. In any case, the discovery of the relatively higher RIS and 9-OH-RIS plasma concentrations in Chinese female patients may be useful in optimizing the clinical treatment protocol for RIS.

The present study shows that the pharmacokinetic parameters of RIS show large interindividual variability in Chinese female patients. This is consistent with the results

of a previous study[26,30]. Variability between patients was notable for RIS, but remained modest for 9-OH-RIS in our study. The reason for this might be that 9-OH-RIS is eliminated by renal excretion, whereas RIS is extensively metabolized by the enzyme CYP2D6, which has high intersubject variability in intrinsic metabolic capacity, despite the fact that there is a much lower incidence of poor metabolizers in the Asian population[31–36]. When the clinically relevant psychoactive moiety, consisting of the sum of RIS plus 9-OH-RIS, was measured, the CV of the pharmacokinetic parameters was lower than that of RIS; ie, there was a reduction in the profound differences in plasma concentrations between individuals.

The absolute bioavailability of RIS is approximately 70% [5,12], which clearly indicates that there is a first-pass effect for RIS. Of note, an earlier study demonstrated that RIS is a substrate of the P-glycoprotein (P-gp), a kind of transmembrane transporter of an ATP-dependent efflux pump for a wide range of drugs[37]. In the human gastrointestinal tract, P-gp is found in high concentrations on the apical surfaces of superficial columnar epithelial cells of the colon and distal small bowel. High levels of P-*gp* are also found on the apical surfaces of epithelial cells in the small biliary ductules, small ductules of the pancreas, proximal ductules of the kidneys, and adrenal glands. P-gp is richly expressed on the subapical surface of the epithelium of the choroids plexus of the brain (which forms the blood-cerebrospinal fluid barrier) as well as the luminal surface of the endothelium of the blood capillaries of the brain (blood-brain barrier)[38–41]. P-gp functions to limit the absorption and, potentially, systemic exposure to its substrates (eg risperidone, cyclosporine, tacrolimus, and talinolol). Intestinal P-*gp* also exhibits wide interindividual variation in its expression (8- to 10-fold)[42]. Whether the metabolizing enzymes (CYP2D6 or CYP3A4) or P-gp, or both primarily contribute to interindividual variability is a topic for further study.

RIS treatment was conducted safely in all 23 subjects. However, in our study RIS treatment resulted in high serum prolactin, which was consistent with previous studies[43,44]. Knegtering *et al* indicated that the plasma concentration of 9-OH-RIS correlated significantly with increases in plasma prolactin[44]. A recent study also showed that plasma concentrations of the RIS active moiety might play a part in predicting the clinical response and occurrence of extrapyramidal symptoms when treating patients with RIS[45]. Therefore, routine therapeutic drug monitoring may be useful to optimize the treatment protocol. For Chinese female patients, an additional investigation with more samples is needed to acquire clearer results.

In conclusion, RIS showed large interindividual variations in pharmacokinetic parameters, indicating that systemic exposure to RIS and 9-OH-RIS in female Chinese schizophrenic patients is higher than that experienced by white Caucasian patients. Doses for individual patients should be carefully titrated and the patients' prolactin levels should be monitored carefully, to minimize side effects. Larger studies regarding the PK/PD relationship might be needed to determine the optimal dose of RIS in Chinese female patients.

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