World Journal of Psychiatry

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World J Psychiatry 2024 April 19; 14(4): 523-532

DOI: 10.5498/wjp.v14.i4.523

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chakrabarti S, India; Pavón L, Mexico

Received: November 21, 2023
Peer-review started: November 21, 2023
First decision: January 24, 2024
Revised: February 7, 2024
Accepted: March 22, 2024
Article in press: March 22, 2024
Published online: April 19, 2024

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Abstract

BACKGROUND

Prior studies have noted great variability in the plasma levels of risperidone (RIS). Plasma concentrations of RIS and its active moiety are highly variable and depend on absorption, metabolism, and other predictors of metabolic dysregulation; however, these factors are poorly understood and the association between metabolic change and change in psychopathology is uncertain.

AIM

To ascertain the characteristics of chronic schizophrenic patients treated with RIS, and to assess their relationship with plasma RIS levels.

METHODS

This was a descriptive cross-sectional study of 50 patients with a diagnosis of schizophrenic psychosis treated with RIS in a psychiatric service. The plasma concentrations of RIS and its metabolite 9-hydroxyrisperidone were determined by high performance liquid chromatography. The patients' demographic and clinical characteristics, and psychopathologies were assessed, and the associations between clinical variables and plasma levels of RIS were explored.

RESULTS
Male patients received higher doses of RIS than female ones, but plasma concentrations of RIS and risperidone + 9-hydroxyrisperidone (active moiety) were higher in female patients. Age and the mean scores of the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS) were significantly positively correlated with plasma concentrations of risperidone + 9-hydroxyrisperidone adjusted for weight and dose in all 50 subjects. In male subjects, we found a statistically significant positive correlation between the concentrations of risperidone + 9-hydroxyrisperidone in plasma/(dose × kg) and age, mean PANSS negative subscale scores, mean PANSS general psychopathology subscale scores, and mean PANSS total scores.

CONCLUSION
Long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects.

Key Words: Antipsychotics; Risperidone; 9-hydroxyrisperidone; Plasma drug concentration monitoring; Chronic schizophrenia

Core Tip: Prior studies have noted great variability in the plasma levels of risperidone (RIS). Fifty patients confirmed to have schizophrenia were selected for this study. We assessed the patients' demographic and clinical characteristic, and psychopathologies, and explored the associations and correlations between clinical variables and plasma levels of RIS. The results of this study indicate that the long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects.

Citation: Xu JW, Guan XB, Wang XY, Feng Y, Zhang Q, Zhu JJ, Chen JH. Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China. *World J Psychiatry* 2024; 14(4): 523-532
URL: https://www.wjgnet.com/2220-3206/full/v14/i4/523.htm
DOI: https://dx.doi.org/10.5498/wjp.v14.i4.523

INTRODUCTION

Schizophrenia is a severe disabling psychiatric disorder which is found in all regions of the world; however, the etiopathology of schizophrenia remains unknown[1]. Antipsychotic medication is a key component of treatment for schizophrenia patients, which acts by stabilizing acute psychotic episodes and preventing recurrences and relapses[2]. Risperidone (RIS) is a second-generation antipsychotic (SGA) with selective antagonistic properties, acting against the serotonin 5-HT2A and dopamine D2 receptors[3]. Currently, RIS is widely applied in the clinical treatment of schizophrenia and a broad spectrum of other psychiatric disorders in China.

RIS is fundamentally metabolized by the hepatic microsomal enzyme cytochrome P450 (CYP)2D6, and, to a lesser extent, by CYP3A4[2]. Its main metabolite, 9-hydroxyrisperidone, is pharmacologically active. Preclinical studies have indicated that 9-hydroxyrisperidone has approximately 70% of the pharmacological activity of RIS[3]. Since the pharmacological activity of 9-hydroxyrisperidone is claimed to be similar to that of the parent compound, the sum of the plasma concentrations of RIS and 9-hydroxyrisperidone is referred to as the clinically relevant "active moiety"[4].

Large intra- and inter-individual variations in plasma concentrations of both RIS and 9-hydroxyrisperidone have been identified in prior studies[2]. Therapeutic drug monitoring (TDM) in the clinic uses the quantification of drug concentrations in plasma or serum to assist physicians in making treatment decisions related to an individual patient. The determination of plasma concentrations of RIS as well as 9-hydroxyrisperidone is used to evaluate patient compliance with the therapy, to optimize treatment, and to minimize the risk of adverse drug reactions (ADRs). By adjusting the dose, a drug concentration associated with the highest probability of response and the lowest risk of ADRs and toxic effects can be achieved. The TDM thus provides a valid method for individual dose titration and careful monitoring, and is strongly recommended in the guidelines for adults treated with RIS[5].

Plasma concentrations of RIS and active moiety are highly variable and depend on absorption, and metabolism, as well as other predictors (for example, age, sex, body mass index, and smoke) of metabolic dysregulation; however, these factors are poorly understood and the association between metabolic change and change in psychopathology is uncertain [6]. Therefore, these factors should be considered in studies.

The primary aim of the present study was to assess the plasma concentrations obtained at different daily doses for the commonly used drug RIS in a natural setting, to examine the clinical situation of patients with chronic schizophrenia treated with RIS, and the possible relations between patient characteristics and plasma concentrations of RIS.

MATERIALS AND METHODS

Study design, sample, and procedures

This was a descriptive transversal study of all the patients treated with RIS in a Psychiatric Hospital with the diagnosis of schizophrenic psychosis. Fifty patients confirmed to have schizophrenia by a group of psychiatrists according to the ICD-10 were selected for this study. None of the patients had serious illness, or current alcohol and/or drug abuse. Patients were treated with oral RIS at doses ranging from 2 to 6 mg/d. The RIS dose was adjusted individually according to the clinical response. The plasma concentrations of RIS and its metabolite 9-hydroxyrisperidone were determined by high performance liquid chromatography (HPLC). Sociodemographic and clinical variables were studied, together with anthropometric measurements, life signs, hemogram, metabolic parameters, and ADRs, between February and March 2021.

HPLC uses a high-pressure infusion pump to pump the specified mobile phase into a chromatographic column containing fillers; the injected sample is brought into the chromatographic column by the mobile phase, and each component is subjected to intermolecular forces in the column. The adsorption-desorption process is carried out between the mobile phase and the stationary phase, so that each component is separated and enters the detector for detecting. A chromatographic signal is recorded and processed by the integrating instrument or the data processing system. In the daily routine testing, the samples are tested in parallel with quality controls, and three quality control concentration levels are used to observe the passing of quality controls. The standard curve graph is prepared, and the data in this study are all between the detectable range of each drug concentration. Chromatographic conditions were as follows: One-dimensional column: AstonSX1 (3.5 mm × 25 mm, 5 μm); intermediate column: Aston SCB (3.5 mm × 10 mm, 5 μm); two-dimensional column: Aston SCB (4.6 mm × 125 mm, 5 μm). The steps of RIS and paliperidone (major metabolite of RIS) detection were: Processing method: ORG-1 1000 μL + blood sample 400 μL, high-speed centrifugation to take the supernatant; detection wavelength: CH1: 276 nm, CH2: 286 nm; flow rate: Pump A: 1.20 mL/min, pump B: 0.01 mL/min, pump C: 0.80 mL/min; temperature: 40 °C; injection volume: 500 μL.

Study variables and scales

The clinical and research staff and participants were not blinded to any of the study conditions, as there was no comparison control group. Clinical interviews were conducted and blood was taken and sent for laboratory analysis. The following parameters were evaluated: An electrocardiogram was performed to evaluate patients' heart rate and QT interval (QTc). Data on patient age, weight, body mass index, blood pressure, and cigarettes smoked per day were also acquired. The discrete evaluated parameters included sex, smoker or not, and taking trihexyphenidyl/laxatives or not (according to the doctor's advice in the medical record) as ADRs occurred. Plasma concentrations of RIS and 9-hydroxyrisperidone were determined while fasting in the morning, without having eaten during the night or taken the breakfast dose of RIS. Using this value, the plasma concentrations of "active moiety" (RIS + 9-hydroxyrisperidone) and concentrations of RIS + 9-hydroxyrisperidone in plasma/(dose × kg) were calculated.

Psychopathological examination, which was completed within 3 d of blood testing, covered the following areas: Psychotic symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS)[7]; depressive symptoms were scored on the Patient Health Questionnaire Depression Scale (PHQ-9)[8], with the results classified as follows: 0-4 points, normal; 5-9 points, mild depression; 10-14 points, moderate depression; and 15-27 points, severe depression.

Statistical methods

All statistical analyses were carried out using IBM SPSS statistics, version 22.0 and GraphPad PRISM, version 7.0. The categorical variables are described as frequencies and percentages, while continuous variables are reported as the mean ± SD or range. Parameters were tested for normal distribution by the one-sample Kolmogorov-Smirnoff test. In the case of continuous variables, the Student's *t*-test was used to compare differences between the averages among groups for two independent samples of normally distributed data, or the Mann-Whitney *U*-test was used to compare data which was not normally distributed. The Pearson correlation coefficient was computed for normally distributed data, and the Spearman rank correlation coefficient was computed for non-normally distributed data. A P value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

A total of 52 patients diagnosed with schizophrenia and treated with RIS were initially enrolled. Of these 52 patients at the time of the study, 2 were excluded for the following reasons: One id not speak and was unable to complete the scales measurement, and the other because of the absence of plasma concentration of RIS. In the end, 50 subjects were included in the study.

The patients were aged from 38 to 69 years old (mean age, 58.4 years, SD = 8.3); 36% (n = 18) were women. All patients had been diagnosed with schizophrenia. Of these, 90% had been in treatment with RIS for more than 5 years, and none had undergone dose changes during the 2 mo prior to the study. Seven (14%) were obese [body mass index (BMI) ≥ 30], while 70% had normal weight (BMI < 25). All smokers (n = 23; 46%) were male, with an average consumption of 16.1 cigarettes/d (SD = 8.8). In the depressive symptom evaluation, three patients (6.0%) showed mild depression, while the

others scored within the normal range according to the PHQ-9 criteria. Details are displayed in Table 1.

Comparisons by sex

The doses of RIS prescribed varied from 2 mg/d to a maximum dose of 6 mg/d, and plasma concentrations of RIS varied from 0 to 43.68 ng/mL, while plasma concentrations of 9-hydroxyrisperidone varied from 10.57 to 98.87 ng/mL. Table 2 shows the dose of RIS and plasma concentrations of RIS and 9-hydroxyrisperidone divided according to gender. Male subjects received higher doses of RIS than female ones, in terms of absolute dose and dose/kg. However, plasma concentrations of RIS and risperidon + 9-hydroxyrisperidone (active moiety) were higher in women, while plasm concentrations of 9-hydroxyrisperidone were higher in men, although these differences were not statistically significant. Statistically significant values in comparison of average plasma concentrations of risperidon + 9-hydroxyrisperidone/dose (Figure 1A) and (dose × kg) according to sex were found (Figure 1B).

Correlation analysis

Regarding the clinical and psychopathological variables, we did not find significant associations between the concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) and any of the variables studied, except for age (P = 0.015, Figure 2) and mean PANSS general psychopathology subscale scores (P = 0.027), which were significantly positively correlated with plasma concentrations of active moiety adjusted for weight and dose in the 50 subjects.

In male subjects (n = 32), a statistically significant positive correlation was found between the concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) and age (P < 0.05), mean PANSS negative subscale scores (P < 0.05), mean PANSS general psychopathology subscale scores (P < 0.05), and mean PANSS total scores (P < 0.05). Regarding female subjects (n = 18), no correlation was found between the average values of plasmatic risperidon + 9-hydroxyrisperidone/(dose × kg) and the clinical and psychopathological variables (P > 0.05, Table 3).

Comparisons of ADRs

Regarding ADRs, anticholinergic or laxative medications were taken according to the doctor's recommendations; such a prescription was indicative of an ADR. Ten of the 50 patients were taking trihexyphenidyl (anticholinergic drug), and there was no statistical difference in each plasma drug concentration variable when compared between the ADR and non-ADR groups (P < 0.05). Among the 50 patients, 10 were taking laxative drugs, and no statistical difference was found in all variables in group comparison (P < 0.05) (Table 4).

DISCUSSION

This study investigated the sociodemographic and clinical characteristics of 55 patients diagnosed with chronic schizophrenia disorder and treated with RIS, in order to clarify any possible associations between these variables and the dosage and plasma concentrations of RIS. Many patients in this study were using RIS for a long time to guarantee blood collections occurring after achieving steady plasma concentrations of RIS and 9-hydroxyrisperidone.

Based on previous studies of groups of patients with chronic schizophrenia, the characteristics of this cohort can be expected: Mostly male, with high rates of smoking, and mainly negative symptoms. However, the small sample size and male predominance could be considered as limitations of this work.

Our study findings show that age was positive correlated with concentrations of RIS + 9-hydroxyrisperidone in plasma/(dose × kg). Some smaller studies have reported slower elimination and/or higher levels of 9-hydroxyrisperidone in the elderly[9-11]. Elimination of 9-hydroxyrisperidone is mainly renal[12], and the most plausible explanation for the accumulation of 9-hydroxyrisperidone in older patients is an age-dependent decline in kidney function. In conclusion, ageing results in a significantly increased dose and weight adjusted plasma concentration of RIS active moiety. This factor must therefore be taken into account when deciding on the dosage in the elderly. The TDM is a good option for dose decisions in this population. If the patient's conditions permit, we recommend measuring plasma RIS and its metabolites in routine clinical practice.

We found that plasma concentrations were significantly higher in women than in men for RIS + 9-hydroxyrisperidone adjusted for dose, as well as for active moiety adjusted for weight and dose, although the men received higher doses of RIS than the women. The same result has been observed in previous studies using SGA[13]. Several factors may explain these sex-related differences, including differences in hepatic clearance of drugs, caused by a lower liver volume in women, while the possible variations in compliance for antipsychotics between males and females should be taken into account[14], although the study was conducted in a hospital setting while all patients are hospitalized. As this was a monocentric study, men received higher doses than women; however, this could be a function of the predominance of men in the relatively small sample; as such, these results may not be generalizable to other settings.

Smoking prevalence in schizophrenic patients is higher than that in the general population[15]. In this study, smoking habits did not appear to influence the plasma concentrations of RIS and 9-hydroxyrisperidone. Berecz *et al*[16] reported that no influence of smoking on RIS metabolism could be found among 40 patients (Berecz *et al*[16] unpublished results). It should be noted that nicotine induces CYP1A2 and CYP2B6 activity, while RIS is extensively metabolized in the liver by CYP3A4 as well as CYP2D6 into the major active metabolite, 9-hydroxyrisperidone[17-19]. This metabolite is the predominant circulating molecule and appears to be of approximately equal efficacy as the parent compound[20]. This may explains why smoking has no influence on RIS metabolism.

Table 1 Characteristics of sociodemographic and clinical variables

Characteristic (*n* = 50)	Minimum value	Maximum value	Mean value	SD
Age (yr)	38	69	58.38	8.31
BMI	16.02	36.05	23.95	4.82
Course of illness (yr)	15	51	33.32	9.18
Systolic blood pressure (mmHg)	90	180	130.08	18.21
Diastolic blood pressure (mmHg)	60	105	78.60	10.32
Heart rate (per min)	60	103	79.86	9.79
QTc	0.38	0.52	0.45	0.03
Mean PANSS positive subscale score	7	20	10.92	3.17
Mean PANSS negative subscale score	9	31	22.32	4.20
Mean PANSS general psychopathology subscale score	22	51	31.04	5.07
Mean PANSS total score	48	101	64.28	8.89
PHQ-9	0	9	1.82	1.64

BMI: Body mass index; QTc: QT interval; PANSS: Positive and Negative Syndrome Scale; PHQ-9: Patient Health Questionnaire Depression Scale.

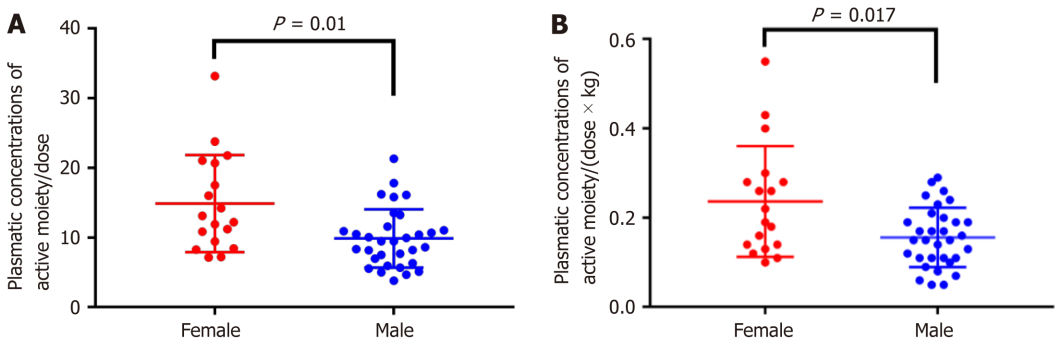

Figure 1 Comparison of concentrations of plasma risperidone + 9-hydroxyrisperidone/dose and plasma risperidone + 9-hydroxyrisperidone/(dose × kg) between males and females. A: Concentrations of plasma risperidone + 9-hydroxyrisperidone/dose (Student's *t*-test); B: Concentrations of plasma risperidone + 9-hydroxyrisperidone/(dose × kg) (Mann-Whitney *U*-test).

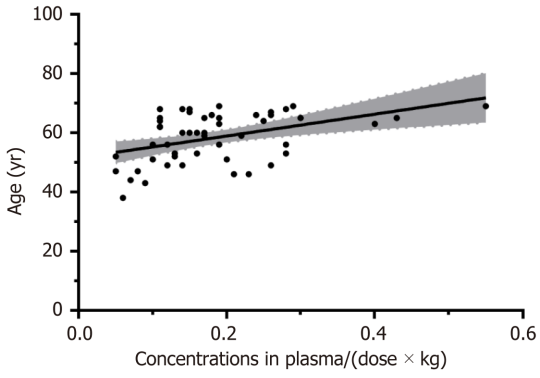

Figure 2 Correlation of sum of steady-state trough risperidon + 9-hydroxyrisperidone concentrations in plasma/(dose × kg) with age for 50 patients (Pearson's correlation coefficient = 0.436, *P* < 0.01).

Table 2 Risperidone dose and plasma concentrations of risperidone and 9 hydroxyrisperidone according to sex

	Sex	*n*	Average	SD	*P* value
Risperidone dose (mg)[1]	Male	32	4.09	1.12	0.003
	Female	18	3.11	0.90	
	Total	50	3.74	1.14	
Risperidone dose per kg weight[2]	Male	32	0.06	0.02	0.010
	Female	18	0.05	0.02	
	Total	50	0.06	0.02	
Concentration of risperidone in plasma (ng/mL)[1]	Male	32	8.61	10.80	0.134
	Female	18	15.13	15.27	
	Total	50	10.96	12.83	
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[1]	Male	32	32.37	18.63	0.887
	Female	18	29.24	10.25	
	Total	50	31.24	16.07	
Concentration of risperidone + 9-hydroxyrisperidone in plasma (ng/mL)[1]	Male	32	40.98	23.98	0.293
	Female	18	44.37	18.79	
	Total	50	42.20	22.11	
Concentration of risperidone + 9-hydroxyrisperidone in plasma/dose[2]	Male	32	9.87	4.18	0.010
	Female	18	14.89	6.96	
	Total	50	11.68	5.81	
Concentration of risperidone + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	Male	32	0.16	0.07	0.017
	Female	18	0.24	0.12	
	Total	50	0.18	0.10	

[1]Mann-Whitney *U*-test.
[2]Student's *t*-test.

The risk of cardiac side-effects by antipsychotic drugs has become a matter of public concern which can result in a prolongation of the QTc on the electrocardiogram[16]. RIS can increase the corrected QTc, although clinically relevant QTc prolongation is rare[21]. In this study, no correlation was found between weight and dose-adjusted concentrations of RIS active metabolite and QTc. This may indicate that RIS at a therapeutically effective plasma concentration does not seem to predispose patients to QTc interval lengthening. Nevertheless, this result has to be interpreted carefully due to the small sample size. One previous study reported that in patients treated with RIS, the QTc was related to CYP2D6 genotypes[22]; however, none of the patients were at risk of arrhythmia.

In our small sample, concentrations of active metabolite adjusted for weight and dose in the steady state were positively correlated with clinical scales, including mean PANSS negative subscale scores, mean PANSS general psychopathology subscale scores, and mean PANSS total scores only in males. We speculated that patients with a higher PANSS score may have more obvious psychiatric symptoms and thus may be prescribed a higher dose of RIS, leading to the higher plasma concentrations of RIS. One prior prospective study found no correlation between serum concentrations of RIS (including sum and ratio of RIS and 9-hydroxyrisperidone) and any other clinical values (*e.g.*, PANSS score)[23]. This prior study involved younger patients without any prior exposure to RIS as a prerequisite. Conversely, the present study was only a cross-sectional study with older subjects who had been taking RIS for a long time and had stable psychiatric symptoms. Therefore, the relationship between RIS concentrations (concentrations of active metabolite adjusted for weight and dose) and psychiatric symptoms in patients (especially among men) with chronic psychosis may need to be clarified with further follow-up.

We chose the use of anticholinergic drugs and laxatives as criteria for ADR, and found no difference between the ADR group and non-ADR group. Our findings are partly consistent with previous data supporting a prominent role of 9-hydroxyrisperidone, but not of RIS, in the development of ADRs[3]. RIS has a high 5-HT2A/D2 ratio, which should protect against extrapyramidal symptoms. However, at higher doses, RIS produces significant EPS, indicating that 5-HT2A antagonism alone cannot eliminate the EPS associated with substantial D2 receptor blockade[24]. In this study, we found that the concentration of 9-hydroxyrisperidone in the ADR group was higher than that of the non-ADR group, although this difference did not reach significance. The metabolite 9-hydroxyrisperidone seems to be the major circulating active moiety, with plasma concentrations 22-fold higher than those of RIS[25]. Clinicians may be advised to

Table 3 Correlation of average concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) according to sex with clinical and psychopathological variables

Correlation of average concentration in plasma/(dose × kg) with	Correlation coefficient	*P* value
Male (n = 32)		
Age (yr)	0.457[2]	0.008
Number of cigarettes (smokers)	-0.359[1]	0.092
Systolic blood pressure	0.096[2]	0.600
Diastolic blood pressure	0.126[2]	0.492
BMI	-0.271[1]	0.134
Heart rate	-0.173[1]	0.344
QTc	0.060[2]	0.743
Mean PANSS positive scale score	0.179[2]	0.328
Mean PANSS negative scale score	0.373[1]	0.035
Mean PANSS general psychopathology subscale score	0.389[1]	0.028
Mean PANSS total score	0.481[2]	0.005
Female (n = 18)		
Age	0.436[1]	0.071
Systolic blood pressure	-0.173[2]	0.492
Diastolic blood pressure	0.024[2]	0.925
BMI	-0.446[2]	0.064
Heart rate	0.132[2]	0.600
QTc	0.059[2]	0.816
Mean PANSS positive subscale score	-0.254[1]	0.310
Mean PANSS negative subscale score	-0.130[2]	0.607
Mean PANSS general psychopathology subscale score	0.375[2]	0.125
Mean PANSS total score	0.064[2]	0.801

[1]Spearman's correlation coefficient.
[2]Pearson's correlation coefficient.
BMI: Body mass index; QTc: QT interval; PANSS: Positive and Negative Syndrome Scale; PHQ-9: Patient Health Questionnaire Depression Scale.

reduce the daily dosage in patients based upon the concentration of 9-hydroxyrisperidone rather than RIS. A further limitation of this study is the lack of an association between EPS and RIS levels. Similarly, we did not find a relationship in this sample between either BMI or blood glucose and plasma concentrations of RIS, which may be attributed to the smaller sample size and long-term RIS administration. As such, further studies with larger samples are needed to draw definite conclusions.

CONCLUSION

To conclude, the results of this study indicate that the long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects. The variability of the dose of RIS, as well as the physical and psychopathological situation of patients underlines the importance of therapeutic monitoring of plasma RIS and 9-hydroxyrisperidone concentrations to adjust the dose of RIS used in patients with chronic schizophrenia. These study findings provide useful insight to understand and address how TDM is necessary in schizophrenic patients receiving RIS while undergoing long-term hospitalization.

Table 4 Comparison between adverse drug reaction groups and non-adverse drug reaction group

	Trihexyphenidyl group (n = 10)	No trihexyphenidyl group (n = 40)	P/Z value
Risperidone dose per kg weight[2]	0.07 ± 0.03	0.06 ± 0.02	0.129
Concentration of risperidone in plasma (ng/mL)[1]	11.18 ± 11.98	10.90 ± 13.18	0.899
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[2]	42.94 ± 26.33	28.32 ± 10.98	0.117
Concentration of risperidon + 9-hydroxyrisperidone in plasma (ng/mL)[2]	54.12 ± 33.68	39.22 ± 17.52	0.205
Concentration of risperidon + 9-hydroxyrisperidone in plasma/dose[1]	11.77 ± 5.67	11.65 ± 5.92	0.923
Concentration of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	0.17 ± 0.08	0.19 ± 0.10	0.577
	Laxative drug group (n = 10)	**No laxative drug group (n = 40)**	***P/Z* value**
Risperidone dose per kg weight[2]	0.06 ± 0.02	0.06 ± 0.02	0.667
Concentration of risperidone in plasma (ng/mL)[1]	11.87 ± 14.22	10.71 ± 12.65	0.971
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[1]	37.77 ± 28.34	29.61 ± 11.20	0.914
Concentration of risperidon + 9-hydroxyrisperidone in plasma (ng/mL)[1]	49.64 ± 36.20	40.35 ± 17.15	0.877
Concentration of risperidon + 9-hydroxyrisperidone in plasma/dose[1]	12.81 ± 6.25	11.39 ± 5.75	0.465
Concentration of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	0.19 ± 0.07	0.18 ± 0.11	0.607

[1]Mann-Whitney *U*-test.
[2]Student's *t*-test.

FOOTNOTES

Co-first authors: Jing-Wen Xu and Xiao-Bo Guan.

Co-corresponding authors: Jian-Hua Chen and Xue-Ying Wang.

Author contributions: Xu JW, Guan XB, Wang XY, and Chen JY conceived, designed, and refined the study protocol, analyzed the data, and drafted the manuscript; Xu JW, Guan XB, and Feng Y were involved in the data collection; Zhang Q contributed to laboratory analysis and electrocardiogram test; Wang XY and Zhu JJ revised and translated the manuscript. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. The reasons for designating Xu JW and Guan XB as co-first authors are twofold: First, they made equal contributions to the writing and revision of the manuscript. Second, this study was conducted collaboratively, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. The rationale behind selecting Chen JY and Wang XY as co-corresponding authors lies in their equal contributions to formulating, conceptualizing, and executing the study. In summary, the co-first and co-corresponding authors in this study not only reflect our team's collaborative spirit and equal contributions, but also enhanced the rationality and depth of the research topic.

Supported by Shanghai Civil Administration Bureau, No. 8-2-50.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Shanghai No. 3 Mental Health Center of Civil Administration.

Informed consent statement: All study participants or their legal guardian provided their consent to participate after being informed of the study's purpose.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request.

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S-Editor: Qu XL
L-Editor: Wang TQ
P-Editor: Zhang YL

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