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Retrospective Study

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

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Abstract

BACKGROUND

Prior studies have noted great variability in the plasma levels of risperidone. Plasmatic concentrations of risperidone and 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 risperidone, and to assess the relationship with risperidone plasma levels.

METHODS

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

RESULTS

The men received higher doses of risperidone than the women, but plasmatic concentrations of risperidone and risperidon+9-hydroxyrisperidone (active moiety) were higher in women. Age and mean PANSS General Psychopathology scores were significantly positively correlated with plasmatic concentrations of risperidon+9-hydroxyrisperidone in plasma adjusted for weight and dose in all 50 subjects. In male subjects we found a statistically significant positive correlation between the concentrations of risperidon+9-hydroxyrisperidone in plasma/ (dose × kg) and age,

Mean PANSS Negative Scale scores, Mean PANSS General Psychopathology scores, and Mean PANSS total scores.

CONCLUSION

Long-term use of risperidone should be closely monitored in older patients and females to minimize the risk of high concentrations.

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

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

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, risperidone is widely applied in the clinical treatment of schizophrenia and a broad spectrum of other psychiatric disorders in China.

Risperidone is fundamentally metabolized by the hepatic microsomal enzymes CYP2D6, 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 risperidone [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 risperidone and 9-hydroxyrisperidone is referred to as the clinically relevant "active moiety" [4].

Large intra and inter-individual variations in plasma concentrations of both risperidone 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 plasmatic concentrations of risperidone as well as 9-hydroxyrisperidone are 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 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 risperidone[5] .

Plasmatic concentrations of risperidone and active moiety are highly variable and depend on absorption, metabolism, as well as other predictors (for example, age, sex, body mass index, smoke, and so on) 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 plasmatic concentrations obtained at different daily doses for the commonly used drug risperidone in a natural setting, to examine the clinical situation of patients with chronic schizophrenia treated

with risperidone, and the possible relations between patient characteristics and plasmatic concentrations.

MATERIALS AND METHODS

Study Design, Sample, and Procedures

This was a descriptive transversal study of all the patients treated with risperidone 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 risperidone doses ranging from 2 to 6 mg/d. The risperidone dose was adjusted individually according to the clinical response. The plasma concentrations of risperidone and its metabolite 9-hydroxyrisperidone was determined by high performance liquid chromatography (HPLC). Sociodemographic and clinical variables were studied, together with anthropometric measurements, life signs, hemogram, metabolic parameters, and adverse drug reactions, 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. Quality control plan: In the daily routine testing, the samples were tested in parallel with quality controls, and 3 quality control concentration levels were used to observe the passing of quality controls. The standard curve graph was prepared, and the data in this study were all between the detectable range of each drug concentration. Chromatographic conditions were as follows: one-dimensional column: AstonSX1(3.5×25mm, 5μm); intermediate column: Aston SCB (3.5×10mm, 5μm); two-dimensional column: Aston SCB (4.6×125mm,

5μm).The steps of risperidone and paliperidone (major metabolite of risperidone) detection: 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 A pump: 1.20 mL/min; B Pump: 0.01 mL/min; Pump C: 0.80 mL/min; Temperature: 40°C; Injection volume: 500 μL.

Study Variables and Questionnaire

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, taking trihexyphenidyl /Laxatives or not (according to the doctor's advice in the medical record) as adverse drug reactions occurred. Plasmatic concentrations of risperidone and 9-hydroxyrisperidone were determined while fasting in the morning, without having eaten during the night or taken the breakfast dose of risperidone. Using this value, the concentrations in plasma of "active moiety" (risperidone+9-hydroxyrisperidone) and concentrations risperidone+9-hydroxyrisperidone in plasma /(dose × kg) were calculated.

Psychopathological examination, which was completed within three days of blood testing, covered the following areas: psychotic symptoms were assessed by means of the positive and negative syndrome scale (PANSS) [7]; depressive symptoms on the PHQ-9 scale (the Patient Health Questionnaire Depression Scale)[8]while the results were classified as follows: 0–4 points indicated normal; 5–9 points was considered mild depression; 10–14 points reflected moderate depression; and 15–27 points represented severe depression.

Statistical methods

All statistical analyses were carried out using IBM SPSS statistics, version 22.0 and the computer software GraphPad PRISM, version 7.0. The categorical variables are described as frequencies and percentages, while continuous variables are reported as means ± 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 risperidone were initially enrolled. Of these 52 patients at the time of the study, 2 were excluded for the following reasons: one patient did not speak and was unable to complete the scales measurement, and one because of the absence of plasmatic concentration of risperidone. 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 risperidone for more than 5 years, and none had undergone dose changes during the 2 months prior to the study. Seven (14%) were obese (BMI ≥ 30), while 70% were normal weight(BMI < 25). All smokers (*n* = 23 ; 46%) were male, with an average consumption of 16.1 cigarettes/day (SD = 8.8). In the depressive symptoms evaluation, 3 patients (6.0%) showed mild depression, while the others scored within the normal range according to PHQ-9 criteria. Details are displayed in Table 1.

Comparisons by sex

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

Correlational analyses

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 scores (P = 0.027),which were significantly positively correlated with plasmatic 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 Scale scores (P<0.05), Mean PANSS General Psychopathology 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 adverse drug reactions

Regarding adverse drug reactions (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 group 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 after group comparison ($P<0.05$) (Table 4).

DISCUSSION

This study investigated the sociodemographic and clinical characteristics of fifty chronic hospital patients diagnosed with schizophrenia disorder and treated with risperidone, in order to clarify any possible associations between these variables with the dosage and plasmatic concentrations of risperidone. Many patients in this study were using risperidone for a long time to guarantee blood collections occurring after achieving steady plasmatic concentrations of risperidone 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 risperidone+ 9-hydroxyrisperidone in the plasma/ (dose × kg) . Some smaller studies have reported slower elimination and/or higher levels of 9-hydroxyrisperidone in the elderly[9,10,11]. 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 plasmatic concentration of risperidone 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 risperidone and its

metabolites in routine clinical practice.

We found that plasmatic concentrations were significantly higher in women than in men for risperidone + 9-hydroxyrisperidone adjusted for dose, as well as for active moiety adjusted for weight and dose, although the men received higher doses of risperidone than the women. The same result has been observed in previous studies used second-generation antipsychotics[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 for schizophrenic patients is higher than for the general population[15]. In this study, smoking habits did not appear to influence the plasmatic concentrations of risperidone and 9-hydroxyrisperidone. LLerena *et al* reported that no influence of smoking on risperidone metabolism could be found among 40 patients (LLerena *et al*, unpublished results) [16]. It should be noted that nicotine induces cytochrome P450 (CYP) 1A2 and CYP2B6 activity, while risperidone is extensively metabolized in the liver by cytochrome P450 3A4 as well as 2D6 into the major active metabolite, 9-hydroxyrisperidone[17,18,19]. 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 risperidone metabolism.

The risk of cardiac side-effects by antipsychotic drugs has become a matter of public concern which can results in a prolongation of the QTc on the electrocardiogram[16] . Risperidone 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 risperidone active metabolite and QTc. This may indicate that risperidone at 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 risperidone, 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 was positively correlated with clinical scales, including mean PANSS negative scale scores, mean PANSS general psychopathology scores, and mean PANSS total scores only in males. We speculated that patients with higher PANSS score may have more obvious psychiatric symptoms and thus may be prescribed a higher dose of risperidone, leading to the higher concentrations in plasma risperidone levels. One prior prospective study found no correlation between serum concentrations of risperidone (including sum and ratio of risperidone and 9-hydroxyrisperidone) and any other clinical values (e.g. PANSS scale) [23]. This prior study involved younger patients without any prior exposure to risperidone as a prerequisite. Conversely, the present study was only a cross-sectional study with older subjects who had been taking risperidone for a long time and had stable psychiatric symptoms. Therefore, the relationship between risperidone 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 risperidone, in the development of ADRs[3]. Risperidone has a high 5-HT2A/D2 ratio, which should protect against extrapyramidal symptoms. However, at higher doses, risperidone 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 in 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 risperidone[25]. Clinicians may be advised to reduce the daily dosage in patients based upon the concentration of 9-hydroxyrisperidone rather than risperidone. A further limitation of this study is the lack of an association between EPS and risperidone levels. Similarly, we did not find a relationship in this sample between either BMI or blood glucose and plasmatic concentrations values, which may be attributed to the smaller sample size and long-term risperidone 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 risperidone 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 risperidone，as well as the physical, psychopathological situation of patients underlines the importance of therapeutic monitoring of plasma risperidone and 9-hydroxyrisperidone concentrations to adjust the dose of risperidone used in patients with chronic schizophrenia. These study findings provide useful insight to understand and address how TDM is necessary in schizophrenic patients receiving risperidone while undergoing long-term hospitalization.

ARTICLE HIGHLIGHTS

Research background

Risperidone is widely applied in the clinical treatment of schizophrenia and a broad spectrum of other psychiatric disorders in China. Prior studies have noted great variability in the plasma levels of risperidone.

Research motivation

Plasmatic concentrations of risperidone and 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.

Research objectives

The aim was therefore to ascertain the characteristics of chronic schizophrenic patients treated with risperidone, and to assess the relationship with risperidone plasma levels.

Research methods

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

Research results

The men received higher doses of risperidone than the women, but plasmatic concentrations of risperidone and risperidon+9-hydroxyrisperidone (active moiety) were higher in women. Age and mean PANSS General Psychopathology scores were significantly positively correlated with plasmatic concentrations of risperidon+9-hydroxyrisperidone in plasma adjusted for weight and dose in all 50 subjects. In male subjects we found a statistically significant positive correlation between the concentrations of risperidon+9-hydroxyrisperidone in plasma/ (dose × kg) and age, Mean PANSS Negative Scale scores, Mean PANSS General Psychopathology scores, and Mean PANSS total scores.

Research conclusions

Long-term use of risperidone should be closely monitored in older patients and females to minimize the risk of high concentrations.

Research perspectives

These findings of the study provide useful insight to understand and address how TDM is necessary in schizophrenic patients receiving risperidone while undergoing long-term hospitalization. Further studies with larger samples are needed to draw definite conclusions.

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