Postprint of Retrospective Analysis of Therapeutic Drug Monitoring Results for Risperidone, 2022–2024

Authors: Liang Lingjun, Zhang Jun, Jianhui Chen, Gao Yongshuang, Yongshuang Gao

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Abstract

Background: Risperidone, as an antipsychotic agent, is widely used in the treatment of schizophrenia and other mental disorders. Although therapeutic drug monitoring (TDM) of risperidone plasma concentrations has been implemented for many years both domestically and internationally, a consensus has not yet been reached regarding the impact of gender and age differences on plasma concentration outcomes.

Objective: To collect risperidone TDM data and analyze the distribution of risperidone TDM across different therapeutic windows and its influence on risperidone plasma concentrations in patients with varying visit types, genders, and ages, thereby providing a medication reference for patients with schizophrenia and other mental disorders treated with risperidone.

Methods: Based on the hospital information retrieval system, basic information including age, gender, plasma concentration data, monitoring frequency, and number of monitoring instances was collected for outpatients and inpatients who underwent risperidone TDM at Zhongshan Third People' s Hospital from 2022 to 2024. According to the therapeutic window range for risperidone recommended by the 2017 Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines for therapeutic drug monitoring (<20 ng/mL as below therapeutic window, 20–60 ng/mL as within therapeutic window, >60 ng/mL as above therapeutic window), categorical statistics were performed to compare the distribution of risperidone TDM across different therapeutic windows and its impact on risperidone plasma concentrations among patients of different years, visit types, age groups, and genders. Data analysis was conducted using SPSS 29.0, and graphs were plotted using Origin Pro 2021.

Results: This study included a total of 2,583 patients with 4,879 monitoring instances, among which 1,738 were female and 3,141 were male. The number of risperidone TDM monitoring instances from 2022 to 2024 demonstrated a year-over-year increase, with a 28.61% increase in 2023 compared to 2022, and a 71.31% increase in 2024 compared to 2022. Among the 2,583 monitored patients, the proportion of outpatients receiving a single monitoring instance was higher than that of inpatients (2=115.48, P<0.001); inpatients receiving two or more than three monitoring instances were higher than outpatients (2=7.22, P=0.007; 2=102.68, P<0.001). No statistically significant difference was observed in risperidone plasma concentrations between outpatients and inpatients (Z=-1.254, P=0.210); risperidone plasma concentrations in male patients were lower than those in female patients (Z=-11.54, P<0.001); a statistically significant difference was found in risperidone plasma concentrations among patients of different age groups (H=36.56, P<0.001). From 2022 to 2024, risperidone TDM was within the therapeutic window for 3,445 instances (70.61%), below the therapeutic window for 471 instances (9.65%), and above the therapeutic window for 963 instances (19.74%). The proportion of monitoring within the therapeutic window was higher than those of the other two categories, with statistically significant differences (2=3,772.19, 2,548.73, P<0.001). A statistically significant difference was observed in the monitored plasma concentrations of risperidone TDM below, within, and above the therapeutic window from 2022 to 2024 (H=1,465.03, P<0.001). Statistically significant differences were found in the distribution proportions of risperidone TDM below, within, and above the therapeutic window among patients of different years, age groups, and genders (P<0.001). The monitored plasma concentrations of risperidone TDM for male, female, and overall samples were 37.4 (26.7, 52.3) ng/mL, 45.3 (32.4, 60.9) ng/mL, and 40.2 (28.6, 55.6) ng/mL, respectively, all within the 20-60 ng/mL range, consistent with the risperidone therapeutic window (20-60 ng/mL) recommended by the AGNP consensus.

Conclusion: In clinical practice, the influence of gender and age differences on risperidone TDM should be considered, and individualized risperidone treatment should be implemented to increase the proportion of plasma concentrations within the therapeutic window. Simultaneously, the application of TDM in the treatment of both outpatients and inpatients should be emphasized to ensure safe and effective clinical medication.

Full Text

Retrospective Analysis of Therapeutic Drug Monitoring Results for Risperidone from 2022 to 2024

LIANG Lingjun[1], ZHANG Jun[2], CHEN Jianhui[1], GAO Yongshuang[1]*

[1]Department of Pharmacy, Zhongshan Third People' s Hospital, Zhongshan 528400, China

[2]The Second People' s Hospital of Hekou District, Dongying 257000, China

Corresponding author: GAO Yongshuang, Chief pharmacist, E-mail: 409632800@qq.com

Abstract

Background: Risperidone, as a first-line antipsychotic agent, is widely used in the treatment of schizophrenia and other mental disorders. Although therapeutic drug monitoring (TDM) of risperidone plasma concentrations has been implemented for many years both domestically and internationally, consensus has not been reached regarding the influence of gender and age differences on plasma concentration results.

Objective: By collecting risperidone TDM data, this study analyzed the distribution of risperidone TDM across different therapeutic windows and the effects of visit type, gender, and age on risperidone plasma concentrations, providing medication reference for patients with schizophrenia and other mental disorders receiving risperidone treatment.

Methods: Using the hospital information retrieval system, we retrospectively collected basic information including age, gender, plasma concentration data, monitoring frequency, and number of monitoring episodes for outpatients and inpatients who underwent risperidone TDM at Zhongshan Third People' s Hospital from 2022 to 2024. Classification and statistical analysis were performed according to the risperidone therapeutic window ranges recommended by the 2017 Consensus Guidelines for Therapeutic Drug Monitoring of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) (<20 ng/mL as below therapeutic window, 20-60 ng/mL as within therapeutic window, >60 ng/mL as above therapeutic window). The distribution of risperidone TDM across different therapeutic windows and its influence on plasma concentrations were compared among patients of different years, visit types, age groups, and genders. Data analysis was performed using SPSS 29.0, and graphs were generated using Origin Pro 2021.

Results: A total of 2,583 patients were included, with 4,879 monitoring episodes conducted, comprising 1,738 episodes in females and 3,141 episodes in males. The number of risperidone TDM episodes increased annually: 28.61% higher in 2023 compared with 2022, and 71.31% higher in 2024 compared with 2022. Among the 2,583 monitored patients, the proportion receiving a single monitoring episode was higher in outpatients than in inpatients (^{2}=115.48, P<0.001), while the proportions receiving 2 or $ 3$monitoringepisodeswerehigherininpatientsthanoutpatients(\chi^{\{2\}=7.22, P=0.007;}\chi\{2\}=102.68, P<0.001).Nostatisticallysignificantdifferencewasobservedinrisperidoneplasmaconcentrationsbet$-1.254, P=0.210).Malepatientsexhibitedlowerrisperidoneplasmaconcentrationsthanfemalepatients(Z=$-11.54, P<0.001).Significantdifferencesinrisperidoneplasmaconcentrationswerefoundamongdifferent

36.56, $P < 0.001$).$From2022to2024, risperidoneTDMwaswithinthetherapeuticwindowin3, 445episodes$(70.61
2,548.73, P<0.001). Significant differences were observed in monitored plasma concentrations across the three categories (H=1,465.03, P<0.001). The distribution proportions across therapeutic windows differed significantly by year, age group, and gender (P<0.001). The monitored plasma concentrations were 37.4 (26.7, 52.3) ng/mL in males, 45.3 (32.4, 60.9) ng/mL in females, and 40.2 (28.6, 55.6) ng/mL overall, all within the 20–60 ng/mL range, consistent with the AGNP consensus-recommended therapeutic window.

Conclusion: In clinical practice, the effects of gender and age differences on risperidone TDM should be considered to implement individualized risperidone treatment, thereby increasing the proportion of plasma concentrations within the therapeutic window. Simultaneously, greater emphasis should be placed on TDM application in both outpatients and inpatients to ensure safe and effective clinical medication use.

Keywords: Risperidone; Therapeutic drug monitoring; Plasma concentration; Schizophrenia; Therapeutic window; Retrospective analysis

Introduction

Risperidone is a first-line antipsychotic medication used for treating schizophrenia and other mental disorders. Research indicates that risperidone plasma concentrations are influenced by dosage, patient age, gender, concomitant medications, pathological conditions, and cytochrome P450 (CYP) 2D6 genetic polymorphisms, and that clinical efficacy and adverse reactions are correlated with plasma concentrations [1]. Therefore, implementing therapeutic drug monitoring (TDM) for patients receiving risperidone may maximize clinical efficacy while minimizing adverse reaction risks.

Currently, TDM is widely implemented across multiple drug classes, including psychiatric medications, cardiovascular drugs, immunosuppressants, antineoplastic agents, and antibiotics. As a branch of clinical pharmacy, TDM employs quantitative analytical techniques to measure drug exposure in the human body, enabling dynamic adjustment of drug dosage or combination regimens based on therapeutic ranges, clinical efficacy, and tolerability to develop precise, individualized treatment plans [2]. In clinical practice, populations with clear indications for risperidone TDM include patients requiring long-term risperidone therapy, those with narrow therapeutic windows, special populations (elderly, pregnant women, children, and those with hepatic or renal impairment), and patients with substantial inter-individual pharmacokinetic and pharmacodynamic variability [2-4].

TDM implementation maximizes clinical medication safety and efficacy while reducing the incidence of potential adverse reactions. Furthermore, by quantitatively monitoring drug exposure, TDM serves as an objective method to assess

patient medication adherence. According to the 2017 AGNP Consensus Guidelines for Therapeutic Drug Monitoring (hereinafter referred to as the AGNP consensus), TDM for risperidone is strongly recommended in clinical practice [2].

Although risperidone plasma concentrations have been monitored via TDM for many years worldwide, consensus regarding the influence of gender and age differences on concentration results remains elusive. Castberg et al. [5] found that age and gender may affect risperidone metabolism, leading to different plasma concentrations at the same dosage. However, other studies have shown no statistically significant differences in the metabolite-to-parent drug concentration ratios between male and female patients in the same age group [6]. Based on risperidone TDM results, this study retrospectively analyzed the overall status of clinical risperidone TDM at Zhongshan Third People' s Hospital, examining the effects of different age groups and genders on TDM results to identify potential influencing factors and provide reference for individualized risperidone therapy.

Methods

Study Design and Participants

Through the hospital information system of Zhongshan Third People' s Hospital, we retrospectively collected basic information for outpatients and inpatients who received risperidone TDM from 2022 to 2024, including age, gender, number of monitoring episodes, monitoring frequency, and raw TDM data. This study was approved by the Ethics Committee of Zhongshan Third People' s Hospital. As the study utilized anonymous retrospective data with minimal risk, informed consent was waived.

Sample Collection

Blood samples were collected from patients receiving risperidone therapy in outpatient or inpatient settings who met the indications for psychiatric TDM. Inclusion criteria were: (1) patients using oral risperidone formulations who had reached steady-state plasma concentrations after continuous administration; (2) blood collection performed in the morning before medication intake. Exclusion criteria were: (1) use of medications affecting risperidone metabolic activity (fluoxetine, duloxetine, paroxetine) prior to sample collection; (2) pregnant or lactating women.

Sample Processing

Blood samples were centrifuged at 4,000 r/min for 5 minutes to separate plasma. A pipette was used to transfer 200 µL of plasma into a 1.5 mL Eppendorf microcentrifuge tube, followed by addition of 500 µL acetonitrile, vortexing for 40

seconds, and centrifugation at 14,000 r/min for 10 minutes at 4°C. The supernatant was then transferred to a 96-well plate using a pipette for quantitative detection by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).

Drug Concentration Measurement

Risperidone plasma concentrations were monitored and analyzed using an established HPLC-MS/MS method [7]. The system consisted of a Shimadzu 8040 LC-MS/MS instrument equipped with a DGU-20A3R automatic degasser, LC-20A binary high-pressure pump, SIL-20AHT-UFLC autosampler, and CTO-20A column oven. The quantitative method for risperidone plasma concentration analysis complied with the 2020 edition of the Chinese Pharmacopoeia [8], with validation of specificity, accuracy, precision, sensitivity, linear range, matrix effects, and stability. All results met the requirements, confirming suitability for risperidone plasma concentration monitoring. Calibrators and quality control samples for risperidone plasma concentration quantification were controllable, with quality control performed according to the established laboratory HPLC-MS/MS method [7].

Therapeutic Window Reference Range

Based on the therapeutic window reference range recommended by the AGNP consensus [below therapeutic window (<20 ng/mL), within therapeutic window (20–60 ng/mL), and above therapeutic window (>60 ng/mL)], the laboratory alert value was set at 120 ng/mL [2]. Risperidone TDM data were statistically analyzed to calculate distribution proportions.

Statistical Analysis

This study used Origin Pro 2021 for graph generation and SPSS 29.0 for statistical analysis. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared between two groups using independent samples t-test or among multiple groups using one-way ANOVA. Non-normally distributed continuous data were expressed as median (25th percentile, 75th percentile) [M(P25, P75)] and compared between two groups using Mann-Whitney U test or among multiple groups using Kruskal-Wallis H test. Categorical data were expressed as relative frequencies and compared using ^{2} test. Statistical significance was set at $P<0.05$.

Results

General Monitoring Status

From 2022 to 2024, 2,583 patients underwent risperidone TDM, with 4,879 monitoring episodes conducted. Male patients accounted for 3,141 episodes

(64.38%), while female patients accounted for 1,738 episodes (35.62%). Patient ages ranged from 11 to 92 years. The number of monitoring episodes increased annually: 28.61% higher in 2023 than in 2022, and 71.31% higher in 2024 than in 2022. Among the 2,583 monitored patients, 363 outpatients underwent 404 monitoring episodes (8.28%), while 2,220 inpatients underwent 4,475 episodes (91.72%). The proportion of patients receiving a single monitoring episode was significantly higher in outpatients than inpatients (^{2}=115.48, P<0.001), whereas the proportions receiving 2 or $ 3*monitoringepisodeswere significantlyhigherininpatientsthanoutpatients*($\chi^{\{2\}= 7.22, P = 0.007; \chi}\{2\}$=102.6
P<0.001) .

Effects of Visit Type, Gender, and Age on Risperidone Plasma Concentration

No statistically significant difference was observed in risperidone plasma concentrations between outpatients and inpatients (Z=-1.254, P=0.210). Male patients exhibited significantly lower risperidone plasma concentrations than female patients (Z=-11.54, P<0.001). Significant differences in risperidone plasma concentrations were found among different age groups (H=36.56, P<0.001), with patients aged 18-60 years showing higher concentrations than those <18 years and >60 years (P<0.001) .

Distribution of TDM Across Therapeutic Windows by Year

From 2022 to 2024, risperidone TDM was within the therapeutic window in 3,445 episodes (70.61%), below the therapeutic window in 471 episodes (9.65%), and above the therapeutic window in 963 episodes (19.74%). The proportion within the therapeutic window was significantly higher than the other two categories (^{2}=3,772.19, 2,548.73, P<0.001). Significant differences were observed in monitored plasma concentrations across the three categories (H=1,465.03, P<0.001). The distribution proportions across therapeutic windows differed significantly by year, age group, and gender (P<0.001). Outpatients had higher monitoring proportions below and above the therapeutic window compared with inpatients, while inpatients had a higher proportion within the therapeutic window (^{2}=16.37, 4.50, 20.04; P<0.001, P=0.034, P<0.001, respectively). This pattern was consistent across individual years .

Distribution of TDM Across Therapeutic Windows by Age Group

Patients were grouped by age: <18 years, 18-60 years, and >60 years. The proportions of TDM within the therapeutic window were 66.67%, 70.87%, and 69.92%, respectively, with the therapeutic window being the predominant category for all age groups. However, the distribution across therapeutic windows differed significantly among age groups (^{2}=43.182, P<0.001) .

Distribution of TDM Across Therapeutic Windows by Gender

Male and female patients showed TDM within the therapeutic window in 72.11% and 67.89% of episodes, respectively, with the therapeutic window being the primary category for both genders. However, the distribution across therapeutic windows differed significantly between genders (^{2}=85.644, P<0.001) .

Comparison of Monitored Concentrations with AGNP-Recommended Therapeutic Window

The monitored risperidone plasma concentrations were 37.4 (26.7, 52.3) ng/mL in males, 45.3 (32.4, 60.9) ng/mL in females, and 40.2 (28.6, 55.6) ng/mL overall. All results fell within the 20–60 ng/mL range, consistent with the AGNP consensus-recommended therapeutic window concentration reference range (20-60 ng/mL), demonstrating good concordance [Figure 1: see original paper].

Discussion

Risperidone, as an antipsychotic medication, is widely used in psychiatric clinical practice for the treatment of schizophrenia and other mental disorders such as bipolar disorder and autism spectrum disorder-related symptoms. In clinical practice, risperidone plasma concentrations are typically maintained within the therapeutic window of 20–60 ng/mL to balance clinical efficacy and tolerability. When plasma concentrations exceed 60 ng/mL, the incidence of adverse drug reactions increases significantly with rising concentrations, whereas concentrations below 20 ng/mL may result in suboptimal therapeutic efficacy [9]. Therefore, implementing TDM for patients receiving risperidone is crucial for improving medication safety, efficacy, cost-effectiveness, and rationality. Previous studies have shown that factors such as gender and age can influence risperidone plasma concentrations, though consensus on their effects remains elusive [10-11]. This retrospective study collected risperidone TDM data from 2022 to 2024 to preliminarily analyze the distribution of risperidone TDM and the effects of different age groups and genders on plasma concentrations, providing reference for individualized therapy during long-term treatment of schizophrenia and other mental disorders.

Our results showed that among 2,583 patients monitored from 2022 to 2024, 1,709 patients (66.16%) underwent TDM only once. Notably, among 363 outpatients, 330 (90.91%) had only a single TDM episode. The proportion of patients receiving single TDM monitoring was significantly higher in outpatients than inpatients, suggesting that empirical medication use is relatively common in psychiatric practice, particularly in outpatient settings. Furthermore, outpatients had a significantly lower proportion of TDM results within the therapeutic window compared with inpatients (P<0.001), and inpatient plasma concentrations differed significantly from those of outpatients (P<0.05), indicating poorer medication adherence among outpatients relative to inpatients. Outpatients may

exhibit poor compliance after discharge, including irregular medication intake, missed doses, or unauthorized discontinuation. Studies have shown that medication adherence in patients with schizophrenia and other mental disorders is closely associated with disease recovery, deterioration, and relapse risk [12-13]. As an emerging monitoring technology, TDM can promptly identify patient medication status and objectively assess adherence based on plasma concentration results, thereby guiding improvements in clinical efficacy. Our findings indicate that while the proportion of risperidone TDM within the therapeutic window did not differ significantly across the three years, the proportion in 2024 increased by 3.70% and 0.62% compared with 2022 and 2023, respectively, suggesting improved responsiveness to individualized TDM in psychiatric patients. In summary, TDM should be strengthened for outpatients to assess recent medication adherence based on concentration results, promptly identify medication issues, and reduce disease recurrence due to adherence problems. For inpatients, TDM implementation based on therapeutic window reference concentrations, integrated with clinical efficacy and tolerability considerations, enables dynamic adjustment of medication dosage or combination regimens to maximize therapeutic effects, minimize adverse reactions, and reduce hospitalization duration.

Regarding gender, our data analysis revealed that female patients had higher risperidone plasma concentrations [45.3 (32.4, 60.9) ng/mL] than male patients [37.4 (26.7, 52.3) ng/mL], consistent with the findings of Guo et al. [14]. Risperidone is primarily metabolized by cytochrome P450 2D6 (CYP2D6) to its active metabolite 9-hydroxyrisperidone (9-OH-RIS). CYP2D6 exhibits genetic polymorphism, and enzyme activity differs between genders, potentially contributing to gender-related differences in risperidone plasma concentrations [15-16]. Additionally, women generally have lower blood volume, smaller body size, and lower body weight than men, which may result in higher drug exposure [17]. Given the lack of large-scale cohort studies on the correlation between risperidone plasma concentrations and Chinese populations, further large-sample studies are needed to investigate and substantiate the influence of gender on risperidone use and to refine gender-specific guidance.

Regarding age, CYP2D6 metabolic capacity may decline with advancing age, though previous studies have reported conflicting findings on the effect of age on CYP2D6 activity [18-19]. Our study found that elderly patients had significantly lower risperidone plasma concentrations than middle-aged and young adult groups, contradicting previous studies reporting higher concentrations in elderly patients [20]. We hypothesize that this discrepancy may be related to correlation between plasma concentrations and administered doses in elderly patients in our study. However, as our study did not investigate the correlation between plasma concentrations and doses, further research is warranted.

Analysis of 4,879 risperidone TDM episodes preliminarily reflects the current status of risperidone TDM. The AGNP consensus suggests that when effective treatment data are unavailable, "therapeutic reference ranges" can be initially established using steady-state trough concentrations ($\bar{x}\pm s$) [21]. However, Hiemke

et al. [21] demonstrated that using M(P25, P75) demonstrates higher concordance with AGNP consensus recommendations than ($\bar{x}\pm s$). Our results showed that risperidone plasma concentrations in males, females, and the overall sample all fell within the 20–60 ng/mL range, consistent with the AGNP consensus recommendation. Moreover, 70.61% of risperidone TDM episodes were within the reference range recommended by the AGNP expert panel, while 29.39% fell outside this range. Based on the 95% medical reference value range formulation rule, our institution' s clinical reference range was determined to be 12.74–97.53 ng/mL, which is broader than the AGNP consensus-recommended range. Therefore, although the majority of our overall sample fell within the AGNP-recommended concentration range, our institution's actual clinical concentration range was wider.

This study has several limitations: (1) The analysis of differences in risperidone TDM results lacked integration with clinical efficacy and tolerability assessments; (2) The analysis of differences in TDM results by visit type, gender, and age did not incorporate factors such as dose, formulation, concomitant medications, comorbidities, or metabolic gene polymorphisms; (3) In the age group analysis, sample sizes for the <18 years and >60 years groups were relatively small compared with the 18–60 years group, potentially introducing bias; (4) This study included only data from our institution and may not represent TDM distribution patterns in other regions of China. Future research should expand sample sizes and conduct more in-depth investigations of relevant influencing factors.

In conclusion, analysis of risperidone TDM data from 2022 to 2024 revealed that age and gender affect patient plasma concentrations, with female patients showing higher TDM-monitored concentrations than male patients. Additionally, while the majority of our institution' s risperidone TDM-monitored plasma concentrations fell within the AGNP-recommended range, our actual clinical concentration range was broader. Therefore, in clinical practice, greater emphasis should be placed on therapeutic drug monitoring to optimize treatment regimens based on plasma concentrations, which holds significance for evaluating patient medication adherence, developing individualized dosing regimens, improving treatment responsiveness, and reducing adverse reaction incidence.

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Author Contributions

LIANG Lingjun: Conceptualization, methodology design, manuscript writing. ZHANG Jun: Standardization and revision of the article. CHEN Jianhui: Data collection, classification, statistical analysis, and graph generation. GAO Yongshuang: Quality review and supervision.

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Conflict of Interest

The authors declare no conflict of interest.

ORCID IDs

LIANG Lingjun: https://orcid.org/0009-0004-7668-7301
GAO Yongshuang: https://orcid.org/0000-0003-0977-5948

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