Effect of the dose regimen on the serum amisulpride concentration and simulation of concentration reference ranges based on population pharmacokinetics

Lu Li
The Affiliated Brain Hospital of Guangzhou Medical University;
Lin Li
The First Affiliated Hospital, College of Medicine, Zhejiang University;
Shan-Qin Huang
The Affiliated Brain Hospital of Guangzhou Medical University;
Hao-Yang Lu
The Affiliated Brain Hospital of Guangzhou Medical University;
Tao Xiao
The Affiliated Brain Hospital of Guangzhou Medical University;
Hong-Zhen Chen
The Affiliated Brain Hospital of Guangzhou Medical University;
Huan-Shan Xie
The Zhuhai Center for Chronic Disease Control, Zhuhai Third People's Hospital;
De-Wei Shang (shang_dewei@163.com)
The Affiliated Brain Hospital of Guangzhou Medical University;
Yu-Guan Wen
The Affiliated Brain Hospital of Guangzhou Medical University;

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Abstract

Aims

This study aims to determine the factors associated the large variability and provided the concentrations reference ranges for different dose ranges.

Methods

A retrospective study was conducted in a psychiatric hospital. The factors associated with the serum amisulpride concentration were examined using multiple linear regression analysis. A comparison of serum amisulpride concentrations among different dose regimens was conducted via analysis of covariance. The amisulpride concentration range for different dosing regimens was simulated using the population pharmacokinetics of Chinese patients with schizophrenia using the Monte Carlo method.

Results

In total, 472 samples from 291 patients were examined to determine the factors associated with amisulpride concentrations. Multiple linear regression analysis indicated that age and the daily dose were positively correlated with the serum drug concentration, whereas male gender and sampling time before the last administration were negative correlated with its concentration. The serum amisulpride concentration significantly differed among the dose regimens. Using an established amisulpride population pharmacokinetic model, the simulated trough concentrations exceeded 320 ng/mL for most regimens with daily doses greater than 600 mg/day.

Conclusion

Differences in dose regimens and daily doses contributed to the large variation of the serum amisulpride concentration. The currently recommended reference does not ensure the attainment of appropriate therapeutic concentrations.

Introduction

Schizophrenia is a complex psychiatric disorder and one of the top 20 causes of disability worldwide. Approximately 1% of the population experiences schizophrenia, which is associated with a significant deterioration of health[1]. Amisulpride is the second most effective among 15 antipsychotic drugs for schizophrenia after clozapine, and it has the lowest risk of all-cause discontinuation. In addition, amisulpride has displayed clinical efficacy over a broad dose range (50–1200 mg/day)[2].

Therapeutic drug monitoring (TDM) is strongly recommended for Amisulpride, and the drug was recommended at the first level by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines, which suggest a therapeutic reference range of 100–320 ng/mL and a laboratory alert level of 640 ng/mL[3]. Plasma/serum amisulpride concentrations display large inter-individual variability, and an obviously higher plasma concentration range was reported in several other studies[4–7]. One study suggested that for the same dosage range, greater than 20-fold inter-individual variation can occur in the drug's steady-state concentration in the body[6].

A system review was conducted to determine the factors associated with the plasma amisulpride concentration using 14 studies from Germany, France, Belgium, the UK, Norway, the Czech Republic, and China. The findings indicated that older female patients always have higher plasma/serum concentrations[8]. In the review, the pooled concentration was significantly higher than the recommended range at a prescribed dose of 594 ± 262 mg/day. However, the concentration/dose ratio (C/D) was within the range suggested by the AGNP (0.47–0.87 [ng/mL]/mg) [3]. It was noted that a high dose may be a primary contributor to the high concentration. However, in Bowskill's study[6], the daily dose explained only 42% of the variation in the plasma amisulpride concentration after log10 transformation of the dose, suggesting that other factors contributed to the high concentration.

Maintaining the plasma drug concentration within an appropriate therapeutic range is an extremely critical issue for pharmacotherapy in patients. In addition to the influence of physiological factors, a study predicting the pharmacokinetic stability of psychiatric drugs following multiple doses indicated that a larger number of doses per day could also contribute to concentration fluctuation (peak-to-trough concentration fluctuations); for example, aripiprazole bid had a lower fluctuation index (FI) than aripiprazole qd (0.081 vs. 0.184) [9]. The FI for amisulpride qd was 1.176, suggesting greater fluctuation. The severity of disease symptoms varies greatly among individuals, resulting in significant differences in daily dosages and regimens. For oral daily doses of 400 mg and higher, amisulpride should be administered twice daily. In clinical practice, various dose regimens are used for amisulpride, as qd, qn, bid, and tid. At present, the therapeutic reference range for amisulpride is 100–320 ng/mL[3], which was supported by only one study of 378 patients dosed once daily[10], and this range significantly differs from the various dose regimens used in clinical practice. However, limited data on the influence of different dose regimens on the plasma amisulpride concentration are available given that only two studies provided information about the dosing regimen[11,12].

Population pharmacokinetic (PPK) modeling has been widely used across many therapeutic areas to identify sources of variability. A PPK modeling approach can identify sources and correlations of pharmacokinetic variability in a target patient population and provide a reliable model to optimize drug therapy for individual patients[13]. Therefore, PPK modeling is an ideal strategy for utilizing TDM data to establish a quantitative model that can be used to guide individualized treatment. Although the incidence of adverse effects of amisulpride is reported to be low, optimizing dosing regimens and suppressing concentration fluctuation using a PPK model might maximize the therapeutic effect of the drug and

reduce its adverse effects. To date, several reports have described PPK models of amisulpride to guide dose adjustments[14,15]. However, little data have been reported for adult Chinese patients with schizophrenia. Therefore, we built a PPK model of amisulpride among Chinese patients with schizophrenia, and the model displayed good predictive efficacy[16]. For decision-making in clinical programs, the use of models and simulation methods to predict treatment outcomes has occupied an increasingly important position. The use of simulation scenarios is a powerful tool for evaluating the impact of multiple concurrent factors on drug exposure, providing a rationale for dose adjustment[17].

To ensure the rational use of amisulpride clinically, the objectives of this study were to clarify the impact of different dose regimens and daily doses on the variability of serum amisulpride concentrations and predict the amisulpride concentration for different dosing regimens based on the estimated PPK model of amisulpride in Chinese patients with schizophrenia.

Results

In total, 472 TDM samples from 291 patients (mean age, 32.9 ± 11.6 years) were eventually included in this study.

The patients included 184 males and 107 females, and 1–8 serum samples were obtained from each patient.
The mean dose was 592.1 ± 223.6 mg/day. None of the patients with severe adverse reactions. The amisulpride concentration and C/D were 362.95 ± 218.69 mg/mL and 0.60 ± 0.32 (ng/mL)/mg, respectively. The most common dose regimen was bid (77.8%), followed by qd (10. 4%), qn (6.6%), and tid (5.3%, Table 1).

Table 1
Comparison of daily doses, concentration and concentration-to-dose (C/D) in patients using Amisulpride by different gender, age group and dosing schedules

Variable	Group	Sample size	Percent(%)	Daily dose (mg/day)	Concentration (mg/mL)	(C/D) ratio
Gender	male	159	33.7%	568 ± 220	325 ± 191	0.57 ± 0.30
	female	313	66.3%	624 ± 225	422 ± 246	0.66 ± 0.35
Age	< 18	15	3.2%	594 ± 217	339 ± 195	0.58 ± 0.31
	18–30	223	47.2%	589 ± 218	338 ± 195	0.58 ± 0.31
	31–40	116	24.6%	657 ± 221	379 ± 207	0.56 ± 0.24
	41–50	69	14.6%	536 ± 223	393 ± 264	0.69 ± 0.35
	51–60	40	8.5%	480 ± 211	352 ± 275	0.68 ± 0.49
	> 60	9	1.9%	600 ± 141	505 ± 213	0.83 ± 0.29
Dose regimen	qd	49	10.4%	278 ± 98	94 ± 81	0.33 ± 0.31
	qn	31	6.6%	287 ± 114	223 ± 154	0.77 ± 0.48
	bid	367	77.8%	651 ± 187	405 ± 204	0.63 ± 0.29
	tid	25	5.3%	720 ± 141	431 ± 228	0.59 ± 0.27
Daily Dose				/		
	200 mg	46	9.7%	/	65.2 ± 42.3	0.32 ± 0.21
	400 mg	128	27.1%	/	263.0 ± 144.3	0.65 ± 0.36
	600 mg	129	27.3%	/	371.7 ± 175.7	0.61 ± 0.29
	800 mg	135	28.6%	/	480.3 ± 196.8	0.60 ± 0.24

Variable	Group	Sample size	Percent(%)	Daily dose (mg/day)	Concentration (mg/mL)	(C/D) ratio
	1000 mg	34	7.2%	/	614.2 ± 213.1	0.61 ± 0.21
Total		472	100.0%	592.1 ± 223.6	362.95 ± 218.69	0.60 ± 0.32
qd: once a day;qn: once a night□bid: twice a day□tid: three times a day						

Multiple linear regression analysis indicated that age (beta = 0.155) and the daily dose (beta = 0.518) were positively correlated with the serum drug concentration. Conversely, male gender (beta = − 0.72) and the sampling time before the last dose (beta = − 0.214) were negatively correlated with the plasma drug concentration (Table 2).

Table 2
Independent correlates of concentration.

Variables	Unstandardized coefficients	Standardized coefficients	t	P value	95.0% CI
	B	Beta			
age	2.90	0.155	4.47	< 0.001	1.62 ~ 4.17
Male gender	-79.3	-0.172	-4.89	< 0.001	-111.1~ -47.5
Daily dose	506.8	0.518	13.1	< 0.001	430.8 ~ 582.7
sampling time before last drug	-14.5	-0.214	-5.4	< 0.001	-19.8~ -9.26
CI: Confidence interval					

The result of ANCOVA suggested that for the same daily dose, the serum amisulpride concentration significantly differed among the dose regimens. The result of post-hoc analysis indicated that at a daily dose of 400 mg/day, the drug concentration was significantly lower for 400 mg qd (121.8 ng/mL vs.326.2 ng/mL, $p < 0.001$) and 200 mg bid (281.5 ng/mL vs.326.2 ng/mL, $p < 0.001$) than for 400 mg qn. No significant difference was observed between 400 mg qn and 200 mg bid ($p = 0.635$). At a daily dose of 600 mg/day, the drug concentration was higher under a dosing schedule of 200 mg followed by 400 mg than for 400 mg followed by 200 mg (421.6 ng/mL vs. 311.8 ng/mL, $p < 0.001$) (Table 3).

Table 3
The association between different dose regime and serum concentration in same daily dose

Daily dose(mg/d)	Dose regimen		Average concentration	test of between subject effects)	
			(mg/mL)	F	Sig
200mg			84.8	2.38	0.084
	qd 200	Once a day,200 mg once	65.2		
	qn 200	Once a night,200 mg once	130.0		
400mg			263.0	1.30	**< 0.001**
	qd 400	Once a day,400mg once	121.8		
	qn 400	Once a night,400mg once	326.2		
	bid 200/200	Twice a day,200mg each time	281.5		
600mg			371.7	4.11	**0.008**
	bid 300/300	Twice a day,300 mg each time	339.7		
	bid 200/400	Twice a day,200 mg followed by 400 mg	421.6		
	bid 400/200	Twice a day,400 mg followed by 200 mg	311.8		
800mg			480.3	2.2	0.13
	bid 400/400	Twice a day,400 mg each time	472.4		
	tid 200/200/400	Three times a day,200 mg and 200mg followed by 400 mg	590.8		
1000 mg			614.2	2.12	0.157
	bid 400/600	Twice a day,400 mg followed by 600 mg	654.0		
	bid 500/500	Twice a day,500 mg followed by 500 mg	530.9		
	bid 600/400	Twice a day,600 mg followed by 400 mg	501.0		

Figure 1 presents the stimulation of concentration distribution after reaching steady state after 5 days of treatment under a fixed dosing regimen. In total, 18 scenarios were evaluated in consideration of the most clinically relevant dosing regimens. The steady-state trough concentration increased as the daily dose increased. For a daily dose of 200 mg, the trough concentrations of amisulpride under qd and qn schedules were 82.0 (90% confidence interval [CI] = 33.6–156.5) and 172.9 ng/mL (90% CI = 108.5–

264.9), respectively. The trough concentration of amisulpride following a 400-mg oral dose was highest for qn administration (345.9 ng/mL [90% CI = 223.5–510.5]), followed by bid with two equal doses (234.7 ng/mL [90% CI = 123.0–397.8]), and the lowest concentration was noted for qd administration (162.1 ng/mL [90% CI = 64.3–318.0). For a daily dose of 600 mg, the trough concentration of amisulpride increased to 351.0 ng/mL (90% CI = 189.3–594.5) following the administration of two 300-mg doses, and the values following bid administration using the 200 mg/400 mg and 400 mg/200 mg schedules were 391.2 (90% CI = 215.3–650.55) and 316.3 ng/mL (90% CI = 158.93–553.9), respectively. For the same daily dose, it was assumed that a higher second dose resulted in a higher plasma concentration. The tough concentration was 339.8 ng/mL (90% CI = 184.2–600.7) following a dose of 200 mg tid. For daily doses of at least 800 mg, the trough concentration under any schedule (bid 400 mg/400 mg; tid 200 mg/200 mg/400 mg; tid 400 mg/200 mg/200 mg)) exceeded 400 ng/mL. For a daily dose of 1000 mg, the trough drug concentration was higher than 500 ng/mL for all bid or tid scenarios.

Discussion

To our knowledge, this is the first study to explore the influence of different dosing regimens using the same daily dose on the blood concentration of amisulpride and to simulate the trough concentration under different regimens using a PPK model, providing an important scientific basis for future clinical application.

Consistent with a previous study[8], although the blood concentration (362.95 ± 218.69 ng/mL) exceeded the range recommended by the AGNP (320 ng/mL), C/D (0.60 ± 0.32) was within the AGNP recommended range of 0.47–0.87 (ng/mL)/mg[3]. In addition, the blood concentration (362.95 ± 218.69 ng/mL) was higher than that (333.9 ng/mL, 95% CI = 294.5–373.3) in a meta-analysis of oral amisulpride[8]. Several factors may have contributed to the high concentration and normal C/D. First, it is inferred that the clinically higher amisulpride blood concentration may be related to the use of higher daily doses. This study recruited patients from a psychiatric hospital, in which patients usually have more severe mental illness than patients in general hospitals. The severity of schizophrenia was associated with the higher daily dose. It is noted that in clinical practice, more attention should be paid to C/D than to the plasma/serum concentration.

In line with the aforementioned study[8], older female patients were more likely to have higher concentrations in our study. Sex-specific pharmacokinetics, such as differences in drug transporter activity[18], probably contributed to the sex differences in the serum amisulpride concentrations. In addition, differences in physiological factors such as lower body weight and organ size in females[19] likely result in higher drug concentrations. In addition to differences in clearance between the sexes, renal function as assessed by creatinine clearance decreases with age. A clinically relevant age-related decline of renal function can be expected in patients older than 65 years[20], which could partly explain the positive association between concentration and age. As the structural and physiological functions of the organs

of elderly patients gradually undergo degenerative changes, more attention should be paid to older patients.

In our study, samples were collected before the next dose, and most TDM data were collected 12 h after the last oral dose, although data were collected 22.5 h after treatment in a small proportion of patients. As assumed that the sampling time after the last dose (beta = − 0.214) was negatively associated with the serum concentration.

The study results illustrated that bid (77.8%) was the most common dosing regimen, in accordance with instructions that amisulpride should be administered bid at a daily dose of 400 mg or higher. Meanwhile, the steady-state trough concentration increased as the daily dose increased. We also found that for the same daily dose, the trough concentration was lowest and the concentration fluctuation was large when the administration interval was 24 h. For higher daily doses, once-daily administration should be avoided as much as possible to increase the therapeutic effect and reduce adverse reactions. Reduced fluctuation can also potentially improve medication adherence in patients who receive antipsychotics for schizophrenia. Using periodic dosage regimens with unequal dosing, the trough concentration increased as the second dose increased. Therefore it is suggested that amisulpride should be administered twice daily using equal doses to avoid excessive concentration fluctuation and ensure better medication compliance.

Actual trough concentrations of amisulpride often exceeded the recommended limit of 320 ng/mL under most scenarios with a daily dose exceeding 600 mg/day, which is consistent with the result of Monte Carlo simulation that the recommended concentration was frequently exceeded under various current dosage regimens with high daily doses. For example, when the simulated dose of 400 was administered qd, 78.6% of the tough concentrations were within the reference range, and 4.75% of the concentrations exceeded the reference range. Under daily doses of 600, 800, and 1000, mg administered in equal two doses, the simulation indicated that 39.7, 14.5, and 5.5%, of the concentrations were within the reference range, respectively, whereas 60.1, 85.3, and 94% of the concentrations exceeded the reference range, respectively.

The concentration range under the existing scheme is only for a single daily dose, which is obviously insufficient. These results suggest that the currently recommended reference range does not ensure the attainment of appropriate therapeutic concentrations. It is necessary to set different dosing ranges for different dosing regimens. The Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology recommended that if valid data on therapeutic reference ranges do not exist, the mean ± SD of drug concentrations in blood of responders to the neuropsychiatric medication should determined[3] and used as a preliminary therapeutic reference range. For a daily dose of 400 mg administered qd and qn, the reference ranges were 94.9–252.1 and 262.3–447.4 ng/mL, respectively. Under daily doses of 600, 800, and 1000 mg administered in equal two doses, the reference ranges were 240.6–493.9, 321.6–652.7, and 401.5–826.9 ng/mL, respectively.

The simulations highlighted the high variability of serum drug concentrations among patients receiving the same dose. Clinical guidelines must consider such covariate effects and ensure appropriate dosing recommendations for adults. If the individual concentration exceeds the reference range, then the patient's actual situation and dose regimens should be considered to provide personalized medication guidance.

Conclusion

This is the first study to confirm the influence of different dose regimens on the serum amisulpride concentration and provide a reference range of concentrations for different regimens based on a PPK model using the Monte Carlo method. The reference ranges developed in this study provide valuable insights into the expected variability in response. Knowledge of these ranges, together with evaluating clinical response, should improve patient outcomes compared with simply targeting a therapeutic range of 100–320 ng/mL per the available guidelines.

This study had some limitations. First, our study was a retrospective, single-center study, and the concentration data were extracted from routine amisulpride TDM data. Second, the reference ranges for the serum amisulpride concentrations were derived from simulations using PPK models created using routine TDM data, which did not consider the relationships of the drug concentration with side effects and effectiveness. Multicenter prospective and fixed-dose cohort studies are needed in the future to provide additional evidence to optimize dosing regimens and provide safe and effective therapy.

Methods

Study population

We conducted a retrospective evaluation of patients with schizophrenia who were treated with amisulpride at a psychiatric hospital between January 1, 2016 and December 31, 2018. The following data were collected using an electronic medical record database in the hospital: age, gender, and biochemical test data. Both the precise sampling time and details of the amisulpride regimen (dosing and administration time) were recorded. The inclusion criteria were as follows: age = 18–65 years; at least 5 days of amisulpride administration (8–10 half-lives), at which time the patients were assumed to have reached steady-state serum concentrations; the measurement of at least one serum drug concentration; and the collection of blood samples shortly before the next dose. The exclusion criteria were as follows: concomitant severe somatic disease; hepatic or kidney impairment; and the receipt of other drugs that can affect the pharmacokinetics or concentration of amisulpride (e.g., clozapine, lithium).All methods were carried out in accordance with relevant guidelines and regulations.

Simulation of amisulpride concentrations for different dosing regimens

To provide specific dose suggestions for Chinese patients treated with amisulpride, we simulated the trough concentration using an established PPK model of amisulpride**.** The population pharmacokinetics

of amisulpride were analyzed via nonlinear mixed-effects modeling using NONMEM with the first-order conditional estimation method with interaction, in which the typical values of apparent clearance and apparent volume of distribution were 52.6 L/h and 885 L^{-1}, respectively. The absorption constant rate of amisulpride was fixed to the literature value of 0.85/h^3. The established model has demonstrated good predictive accuracy[16]. We simulated the trough concentration using the Monte Carlo method based on the established PPK model under scenarios in which 400, 600, 800, and 1000 mg of amisulpride were administered using various dosing intervals (qd, qn, bid, and tid). Two thousand simulations were performed, and the steady-state concentration of each simulated subject was calculated.

Statistical analyses

Data analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA) for Windows. Multiple linear regression analysis using the “enter” method was performed to determine the independent factors correlated with the serum amisulpride concentration. In the analysis, the serum amisulpride concentration was entered as the dependent variable, whereas gender, age, the sampling time before the last dose, and the daily dose were the independent variables. The significance level was set at 0.05 (two-sided) to avoid collinearity between the sampling time before the last dose and the dose regimen, and only the sampling time before the last dose was entered into the model. After controlling for confounders (age, gender, sampling time before the last dose), the serum amisulpride concentration was compared among different dose regimens at the same daily dose via analysis of covariance (ANCOVA).

Declarations

Ethics approval. Procedures were in accordance with Declaration of Helsinki and approved by the Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University. The requirement for informed consent was waived by the ethics committee that approved the study, owing to the retrospective nature of the analyses.

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None

Author contributions:

Study design: Lu Li, DW Shang, Data collection: HY Lu, SQ Huang, HS Xie, Analysis and interpretation of data: Lin Li, Lu Li, HZ Chen, T Xiao, Drafting of the manuscript: Lin Li, Lu Li, Critical revision of the manuscript: DW Shang, YG Wen, Approval of the final version for publication: all authors.

Conflict of interest statement

There are no competing interests to declare.

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Data availability statement

Data used in this analysis will be provided freely through the Open Science Framework upon completion of the study.

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Figures

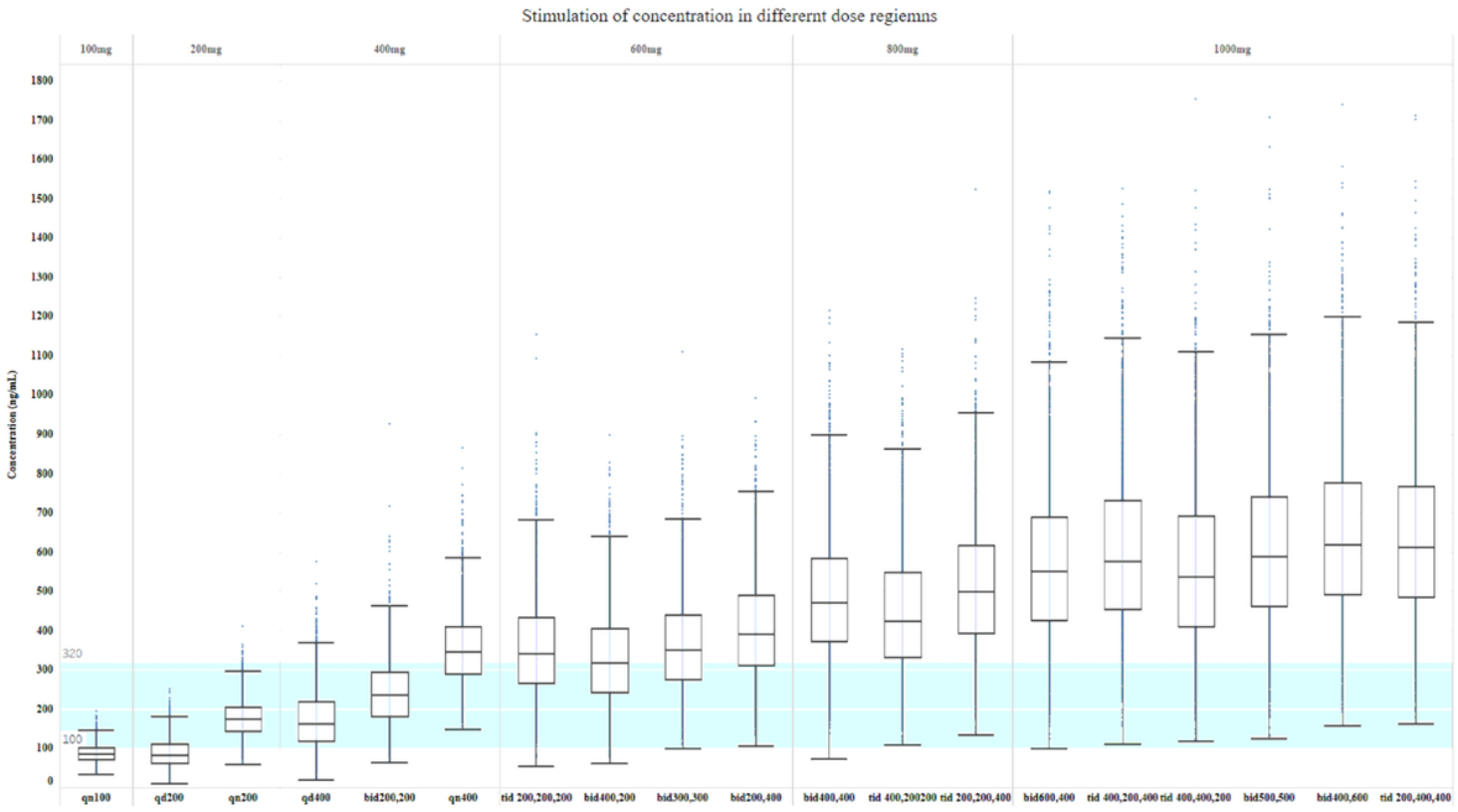

Figure 1

Whisker-box plots show the median, quartiles and 90% prediction intervals for the steady-state concentrations achieved in adults receiving different doses and dosing regimens of amisulpride.