

Original Article

Influences of *CYP2D6*10* polymorphisms on the pharmacokinetics of iloperidone and its metabolites in Chinese patients with schizophrenia: a population pharmacokinetic analysis

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Aim: Iloperidone is an atypical antipsychotic drug that is mainly metabolized by CYP2D6, CYP3A4, and cytosolic enzymes. Previous studies show that extensive and poor metabolizers of CYP2D6 exhibit different plasma concentrations of iloperidone and its metabolites. The aim of this study was to develop a parent-metabolite population pharmacokinetic (PPK) model to quantify the effects of *CYP2D6*10* allele on the pharmacokinetics of iloperidone and its metabolites in Chinese schizophrenia patients.

Methods: Seventy Chinese schizophrenia patients were enrolled, from whom limited blood samples were collected on d 15 (0 h) and d 28 (0, 4 and 12 h after drug administration). The plasma concentrations of iloperidone and its metabolites M₁ (P-88) and M₂ (P-95) were simultaneously detected using a validated HPLC-MS assay. *CYP2D6*10* (rs1065852) genotyping was performed. A PPK model was developed based on data from the patients using the NONMEM software (version 7.2). A one-compartment model with first-order absorption and elimination was used to describe the pharmacokinetic data related to iloperidone and its metabolites.

Results: Patients with the *CYP2D6*10* T/T genotype had significantly higher concentrations of iloperidone and M₁, and lower concentrations of M₂ than the patients with C/C or C/T genotypes. The *CYP2D6*10* genotype affected the elimination constants for transformation of iloperidone to the metabolites M₁ (K₂₃) and M₂ (K₂₄). The K₂₃ value of the patients with T/T genotype was 1.34-fold as great as that of the patients with C/C or C/T genotype. The K₂₄ value of the patients with C/T and T/T genotypes was 0.693- and 0.492-fold, respectively, as low as that of the patients with C/C genotype.

Conclusion: *CYP2D6*10* mutations affect the pharmacokinetics of iloperidone and its metabolites in Chinese schizophrenia patients, suggesting that the clinical doses of iloperidone for patients with *CYP2D6*10* mutations need to be optimized.

Keywords: schizophrenia; iloperidone; gene polymorphisms; *CYP2D6*10*; population pharmacokinetics

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Introduction

Iloperidone is an atypical antipsychotic drug that was approved in 2009 by the Food and Drug Administration (FDA) for the acute treatment of schizophrenia in adults with a high 5-hydroxytryptamine 2a/dopamine 2 (5-HT_{2a}/D₂) receptor antagonist ratio, which results in a relatively low risk of extrapyramidal side effects (EPS)^[1, 2]. The therapeutic reference

range of iloperidone is relatively narrow at 5–10 ng/mL as defined by the therapeutic drug monitoring (TDM) group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP)^[3].

Iloperidone undergoes extensive pre-systemic elimination and is cleared through multiple metabolic pathways that include *O*-dealkylation, hydroxylation, decarboxylation/oxidation and reduction^[4, 5]. Two major metabolites of iloperidone (M₁, also termed P-88 and M₂, also termed P-95) have higher plasma concentrations in humans than iloperidone, although the exact fractions of M₁ and M₂ formation from the parent iloperidone have not yet been identified. M₁ may contribute to the therapeutic profile of iloperidone because it

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exhibits receptor-binding affinities that are similar to those of the parent compound. Unlike M_1 , M_2 is unlikely to add to the therapeutic profile of iloperidone due to its low affinity for the 5-HT_{2a} receptor^[6]. The roles of CYP2D6, CYP3A4, and other enzymes in iloperidone metabolism have been investigated^[7]. M_2 is a hydroxylation metabolite of iloperidone that is produced by CYP2D6. Cytosolic and microsomal enzymes are related to M_1 . The *O*-demethylation metabolites are produced by CYP3A4.

The pharmacokinetic parameters of iloperidone and its metabolites (M_1 and M_2) differ between extensive metabolizers (EM) of CYP2D6 and poor metabolizers (PM) of CYP2D6. For example, the iloperidone plasma exposure is higher in PMs than in EMs, and the elimination half-time ($t_{1/2}$) of iloperidone is 33 h or longer in PMs^[7]. Additionally, CYP2D6 polymorphisms (*10, *5) affect the pharmacokinetic parameters of other atypical antipsychotic drugs, such as risperidone^[8] and aripiprazole^[9]. The allele frequencies of CYP2D6*10 (rs1065852, allele C>T) mutations are 48%–70%^[10] and 30%–50%^[11] in Chinese and other Asian populations (eg, Japanese and Korean populations), respectively. However, the effects of the CYP2D6*10 (rs1065852) mutation on the pharmacokinetics of iloperidone in clinical practice remain unknown.

Compared to healthy volunteers, it is difficult to perform classic pharmacokinetic studies with rich blood samples from patients due to ethical considerations and the low recruitment rate in clinical practice. Hence, population pharmacokinetics (PPK) is a better choice for pharmacokinetic studies of patients with limited available sampling points. Additionally, PPK analyses help to quantitatively define the degree and influence of covariates on pharmacokinetic parameters. For example, PPK models have been developed for risperidone to investigate the influences of the CYP2D6 genotype and other factors on the pharmacokinetics of risperidone^[12–14].

The aims of this study were to develop a parent-metabolite PPK model of iloperidone and its metabolites in Chinese patients with schizophrenia and to identify the extent of the contribution of the CYP2D6*10 (rs1065852) mutation to the variabilities in the PKs of iloperidone and its metabolites to guide clinical dosage optimization.

Materials and methods

Patients and study design

Multiple-center clinical trials were conducted at 13 hospitals in China. The study protocol was designed and performed according to the Declaration of Helsinki and the International Conference Harmonization Guidelines for Good Clinical Practice. Informed consent was obtained from all patients enrolled in the study. Eligible patients included male and female patients between 18 and 65 years of age with a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification. Patients were excluded if they had previously exhibited no positive treatment effects with sufficient drug commitment to psychoactive substances, had received clozapine or other depot antipsychotics in the last three

months, were pregnant, or had a history of alcohol or drug abuse, epilepsy, tardive dyskinesia or brain disease.

Based on previous studies^[7], the patients' doses were titrated from 2 to 12 mg/d (2 mg/d on d 1, 4 mg/d on d 2, 8 mg/d on d 3 and 12 mg/d on d 4; twice daily dose regimen). The exact dosing scheme for each patient was recorded.

According to the FanaptTM (iloperidone tablets) label^[15], the recommended target dosage of iloperidone is 12 to 24 mg/d administered twice daily (12 mg/d, 16 mg/d, 20 mg/d or 24 mg/d). Based on the patient's tolerance to iloperidone, dose adjustments were performed on d 5–14 after administration of the first dose. The fixed dose after the adjustment was taken on d 15–28. Dosing records were implemented according to individually recorded dosing schemes.

Sampling

Four blood samples were collected, including one on d 15 (C_{15-0} , taken on the first day of fixed-dosing) and three on d 28 (C_{28-0} , taken before drug administration in the morning; C_{28-4} , taken 4 h after drug administration in the morning; and C_{28-12} , taken 12 h after drug administration in the morning). An additional 10-mL blood sample was obtained from each patient for CYP2D6*10 genotyping. The plasma concentrations of iloperidone and its metabolites M_1 (P-88) and M_2 (P-95) were simultaneously determined using a validated high-performance liquid chromatography-mass spectrometry assay^[16, 17]. The linear ranges were 1–100 and 3–120 ng/mL for iloperidone and its metabolites, respectively. The limits of detection were 1 and 3 ng/mL for iloperidone and metabolites, respectively. The extraction recovery rates of the method were greater than 90% without matrix effects.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using a Wizard[®] Genomic DNA Purification kit (Promega Corporation, Madison, United State of America) with Technical Manual TM050. CYP2D6*10 (rs1065852) genotyping was performed using the gene sequencing method. The following primer set was used: forward primer, 5'-CATTTG-GTAGTGAGGCAGGTAT-3'; reverse primer, 5'-CCTT-GCCCTACTCTTCCTTG-3'.

Data analysis

The subjects' data are presented as the mean±the standard deviations (SD) or ranges. The concentrations were normalized to the doses (concentration/dose, *C/D*). Differences in the *C/D* ratio and the pharmacokinetic parameters between the different CYP2D6*10 genotypes were assessed using multiple linear regression and account for the influence of body weight.

Population pharmacokinetic (PPK) modeling

The data were graphically presented using R (3.0, <http://www.r-project.org>). The nonlinear mixed-effects modeling software program NONMEM (7.2, ICON Development Solutions, USA) with PSN (3.7.6 <http://psn.sourceforge.net/index>).

php) was used to develop the PPKs of iloperidone and its metabolites with the ADVAN 6 subroutine using a first-order conditional estimation method with an η - ϵ interaction.

Both one-compartment and two-compartment structural models with first-order absorption models (with and without an absorption lag time) were tested. However, the one-compartment model with first-order adsorption and elimination was finally used for the parameter estimations of iloperidone and its metabolites in the current study due to the limited blood samples in this study, the limited information about the pharmacokinetics of iloperidone, and the large relative standard errors (RSEs, >50%) or condition numbers (>1000) of the other structural models. A schematic diagram of the model of iloperidone and its metabolites is presented in Figure 1. First, the sequential approach was applied to fit the pharmacokinetics of iloperidone and its metabolites, and a combined model of iloperidone and metabolites was then performed in a simultaneous manner based on the results from the sequential modeling. Because the relative molecular masses of M_1 (429.4 g/mol) and M_2 (429.2 g/mol) are both very close to that of iloperidone (427.3 g/mol), the mass units rather than the molar units were used for convenience. Due to the lack of a conversion fraction for iloperidone to its metabolites (M_1 and M_2), the pharmacokinetic parameters for M_1 (K_{23} , the formation rate constants of M_1 , and K_{30} , the elimination rate constants of M_1) and for M_2 (K_{24} , the formation rate constants of M_2 , and K_{40} , the elimination rate constants of M_2) were simultaneously estimated after setting both V_3 (the volume of the distribution of M_1) and V_4 (the volume of the distribution of M_2) at 10 L. Proportional, additional, and combined proportional and additional error models were evaluated to describe the residual variability.

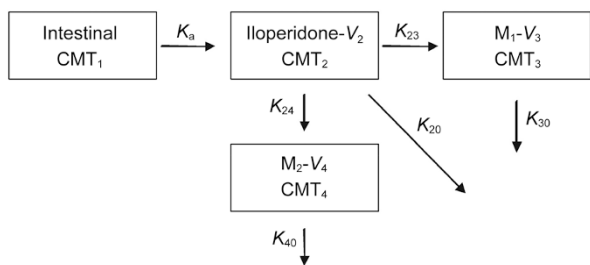


Figure 1. Scheme of the structural model of iloperidone, M_1 and M_2 . K_a is the absorption constant of iloperidone, K_a was set at 2.26 h^{-1} ; K_{23} and K_{24} represent formation rate constants of M_1 and M_2 , respectively; K_{20} is the elimination rate of iloperidone by other elimination pathways; ($K_{20}+K_{23}+K_{24}$) is the elimination of iloperidone; $K_{23}/(K_{20}+K_{23}+K_{24})$ is the conversion fraction rate of iloperidone; K_{30} and K_{40} represent the elimination rate of M_1 and M_2 , respectively; CMT₂, CMT₃, and CMT₄ represent compartment of iloperidone and metabolites; V_2 , V_3 , and V_4 represent the volume of distribution of iloperidone and metabolites.

The covariates in the model construction included demographics, *CYP2D6*10* genotype, physiological and biochemical indices obtained before administration, including red blood

corpuscle (RBC), total protein, serum creatinine, uric acid and other values. Correlations between any pair of variables were identified through correlation analysis.

Continuous covariates were tested using either the linear [Eq (1)] or power [Eq (2)] equation listed below (using RBCs as an example):

$$K_{24} = TV(K_{24}) * (1 + \theta_1 (RBC - RBC_m)) * \exp(\eta K_{24}) \quad (1)$$

$$K_{24} = TV(K_{24}) * (RBC / RBC_m)^{\theta_1} * \exp(\eta K_{24}) \quad (2)$$

where $TV(K_{24})$ is the typical value of the formation rate constant of M_2 (K_{24}) for a patient with the median value for the covariate (RBC_m). θ_1 is the estimated influence factor for RBCs. ηK_{24} is the random between-subject variability.

For categorical covariates, such as the *CYP2D6*10* genotype, the effect of the covariates on the K_{24} is expressed as follows:

$$\text{IF (genotype.EQ.2)} \quad K_{24} = \theta_1 * TV(K_{24})$$

$$\text{IF (genotype.EQ.3)} \quad K_{24} = \theta_2 * TV(K_{24})$$

where genotype represents *CYP2D6*10*. We set *CYP2D6*10* C/C (ie, the wild-type homozygote), C/T (ie, the heterozygote), and T/T (ie, the mutant homozygote) as 1, 2, and 3, respectively. $TV(K_{24})$ is the typical K_{24} value in patients with the *CYP2D6*10* C/C genotype; K_{24} in patients with the *CYP2D6*10* C/T genotype was $\theta_1 * TV(K_{24})$, and this value in patients with the *CYP2D6*10* T/T genotype was $\theta_2 * TV(K_{24})$.

Stepwise forward addition followed by backward elimination processes were used to build the final model. The criteria for addition and elimination were a minimal objective function value (OFV) decrease of >3.84 ($P < 0.05$, $df=1$) or 5.99 ($P < 0.05$, $df=2$) and an OFV increase of >6.63 ($P < 0.01$, $df=1$) or 9.21 ($P < 0.01$, $df=2$), respectively.

The following goodness-of-fit plots were used to validate the PPK model: the population predicted (PRED) and individual predicted (IPRED) values versus the observed concentrations (DV), and the PRED versus the conditional weighted residuals (CWRES). A nonparametric bootstrap approach and a standard visual predictive check (SVPC) were used to validate the model.

Results

A total of 70 patients with acute psychotic episodes met the inclusion criteria, and all of these patients completed the study. The *CYP2D6*10* alleles (rs1065852) were detected. Eleven patients carried the *CYP2D6*10* C/C genotype, 42 patients carried the C/T genotype, and 17 patients carried the T/T genotype. Four patients (3 C/T and 1 T/T) took iloperidone at a dose of 12 mg/d, 12 patients (2 C/C, 7 C/T and 3 T/T) took 16 mg/d, 24 patients (1 C/C, 18 C/T and 5 T/T) took 20 mg/d, and 30 patients (8 C/C, 14 C/T and 8 T/T) took 24 mg/d after the dose adjustments. The main patient characteristics are presented in Table 1.

Pharmacokinetic data

In total, 804 concentration measurements (266 for iloperidone, 268 for M_1 , and 270 for M_2) were implemented in the PK analysis. The C/D ratios of iloperidone and its metabolites differed

Table 1. Basic characteristic for patients. ^aValues are expressed as mean±SD or mean (ranges) and *n*=70.

Characteristics	Values ^a (<i>n</i> =70)	Dose			
		12 mg/d (<i>n</i> =4)	16 mg/d (<i>n</i> =12)	20 mg/d (<i>n</i> =24)	24 mg/d (<i>n</i> =30)
Age (year)	34±12	38±4	34±14	36±13	31±10
Height (m)	1.64±0.07	1.63±0.07	1.64±0.05	1.62±0.06	1.66±0.08
Weight (kg)	62.2±10.5	70.4±6.6	59.9±10.2	59.6±9.4	64.1±11.3
BMI	23.1±3.5	26.6±3.1	22.2±3.6	22.6±3.5	23.3±3.45
Gender (<i>n</i>)					
Male	28	2	2	7	17
Female	42	2	10	17	13
CYP2D6*10 (%)					
C/C	11 (15.71%)	0	2	1	8
C/T	42 (60.00%)	3	7	18	14
T/T	17 (24.29%)	1	3	5	8
Red blood corpusle (10 ¹² /L)	4.5±0.5 (10.8, 75)				
Asparate aminotransferase (U/L)	24.2±2.0 (10.8, 75)				
Alanine aminotransferase (U/L)	22.2±13.9 (5.4, 95)				
Total bilirubin (mmol/L)	13.9±6.0 (6.1, 32.8)				
Direct bilirubin (mmol/L) [#]	3.9±1.5 (1.4, 8)				
Blood urea nitrogen (mmol/L)	4.8±1.9 (1.83, 13.8)				
Serum creatinine (mmol/L)	63.6±12.0 (42, 93.4)				
Number of patients with history of medicine administration (male/female)			9/17		

[#]Values are obtained from 64 patients.

between the *CYP2D6*10* genotypes, as presented in Figure 2. Specifically, the *C/D* ratio of iloperidone to M_1 in patients with the *CYP2D6*10* T/T genotype was greater than those in patients with the C/C and C/T genotypes. However, the *C/D* ratio for M_2 in patients with the *CYP2D6*10* T/T genotype was lower than those in patients with the C/C and C/T genotypes. Statistically significant differences were found in the C_{28-12}/D ratio of iloperidone, the C_{28-0}/D , C_{28-4}/D , and C_{28-12}/D ratios of M_1 , and the C_{15-0}/D and C_{28-0}/D ratios of M_2 between the *CYP2D6*10* genotypes.

Population pharmacokinetic (PPK) models

A one-compartment model with first-order absorption and elimination was sufficient to simultaneously describe the plasma concentrations of iloperidone and its two metabolites. The absorption rate constant K_a was estimated to be 2.26 h⁻¹. The estimated parameters included K_{23} , K_{24} , K_{30} , K_{40} , the volume distribution of iloperidone (V_2), and the elimination rate of iloperidone by other elimination pathways (K_{20}). Exponential and proportional models were used to describe inter-subject and residual variabilities, respectively.

In the forward model building step, the *CYP2D6*10* and RBC parameters decreased the OFV by more than 3.84 or 5.99 ($P<0.05$) at each addition. The *CYP2D6*10* mutation significantly affected the K_{23} and K_{24} . The RBC influenced the volume of iloperidone.

Significant increases in the OFV of more than 6.63 or 9.21

($P<0.01$) were produced in the backward elimination step of the model. The *CYP2D6*10* genotypes were retained in the final model. The RBC level was excluded in the final model because it resulted in an OFV increase of 3.993, which was less than 6.63. The PPK modeling process and the detailed parameters of the final model are presented in Table 2.

The K_{23} of M_1 was affected by the *CYP2D6*10* genotypes as illustrated by the following equation: $(K_{23})_i = \theta * 0.00451 * \exp(\eta_i)$. When patients carried the *CYP2D6*10* C/C or C/T mutations, $\theta=1$, and when patients carried the T/T genotype, $\theta=1.34$. η_i was the difference between the estimated value and the typical K_{23} value.

The K_{24} of M_2 was affected by the *CYP2D6*10* genotypes as illustrated by following equation: $(K_{24})_i = \theta * 0.00649 * \exp(\eta_i)$. When patients carried the *CYP2D6*10* C/C mutation, $\theta=1$; when patients carried the *CYP2D6*10* C/T mutation, $\theta=0.693$; and when patients carried the T/T genotype, $\theta=0.492$. η_i was the difference between the estimated value and the typical K_{24} value.

Model validation

Goodness-of-fit plots for the final pharmacokinetic model are provided in Figure 3. The individual- and population-predicted plasma concentrations of iloperidone and its metabolites matched the observed plasma concentrations, which indicates that the model describes the data very well. As illustrated in Figure 3, an acceptable range (-2 to 2) was found

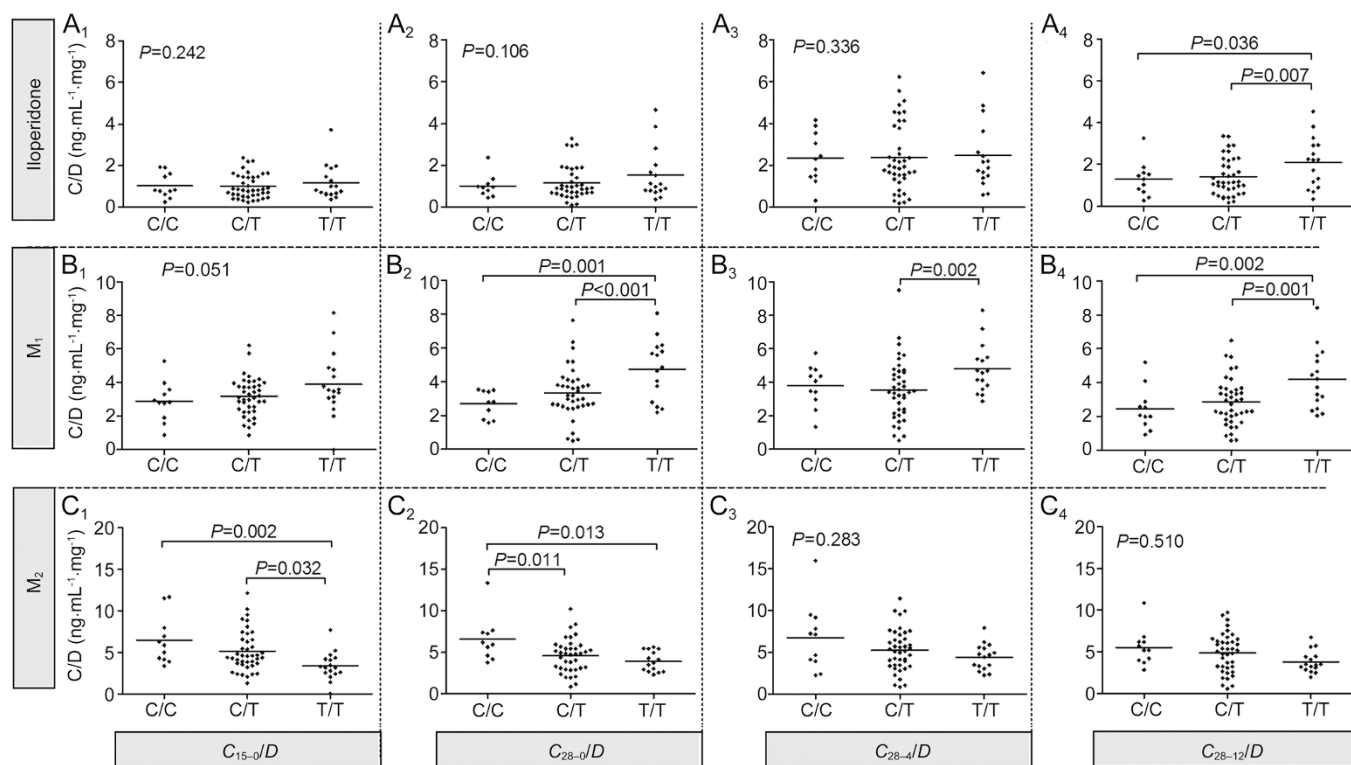


Figure 2. Concentration/Dose ratio of iloperidone, M_1 , and M_2 separated by $CYP2D6^*10$ genotype. C/D is the concentration/dose ratio; A, B, and C represent figures for iloperidone, M_1 , and M_2 , respectively; C/C, C/T, and T/T represent $CYP2D6^*10$ genotypes. P -values are from multiple linear regression (corrected by body weight).

Table 2. Population pharmacokinetic modeling process.

N_q	Model description	OFV	Δ OFV
Model building			(df=1, $P=0.05$, 3.84) (df=2, $P=0.05$, 5.99)
1	1-Compartment base model	4568.535	
2	Add $CYP2D6^*10^2$ on K_{24} in model 1	4547.571	-20.964
3	Add $CYP2D6^*10^1$ on K_{23} in model 2	4537.103	-10.468
4	Add RBC on V_2 in model 3	4531.905	-5.198
Model elimination			(df=1, $P=0.01$, 6.63)(df=2, $P=0.01$, 9.21)
5#	Remove RBC on V_2 in model 4	4537.103	-5.198
6	Remove $CYP2D6^*10^1$ on K_{23} in model 4	4547.168	15.263
7	Remove $CYP2D6^*10^2$ on K_{24} in model 4	4540.699	8.794

OFV, objective function value; RBC, red blood corpuscle; $CYP2D6^*10^1$ data divided into two groups: $CYP2D6^*10$ (C/C+C/T) vs T/T; $CYP2D6^*10^2$ data divided into three groups: $CYP2D6^*10$ C/C vs C/T vs T/T. # Final model.

in which the conditional weighted residuals (CWRES) were randomly distributed around zero, which demonstrates that the CWRES did not reflect any particular systematic trends.

The mean parameter estimates and 95% CIs from the bootstrap analysis are presented in Table 3. The covariance step was 92.6% successful. There were no statistically significant differences from the estimates based on the original dataset. The variability estimates from the bootstrap analysis were similar to the estimates from the original data. Figure 4 illus-

trates the SVPC of the pharmacokinetic model of iloperidone and its metabolites. The open circles represent the calculated $P_{i,j}$ values obtained from 1000 simulated datasets for each observation versus time.

Influence of $CYP2D6^*10$ on the clearance of iloperidone and the PPK parameters

The clearance of iloperidone was not markedly affected by the $CYP2D6^*10$ genotypes, but the K_{23} and K_{24} values were notably

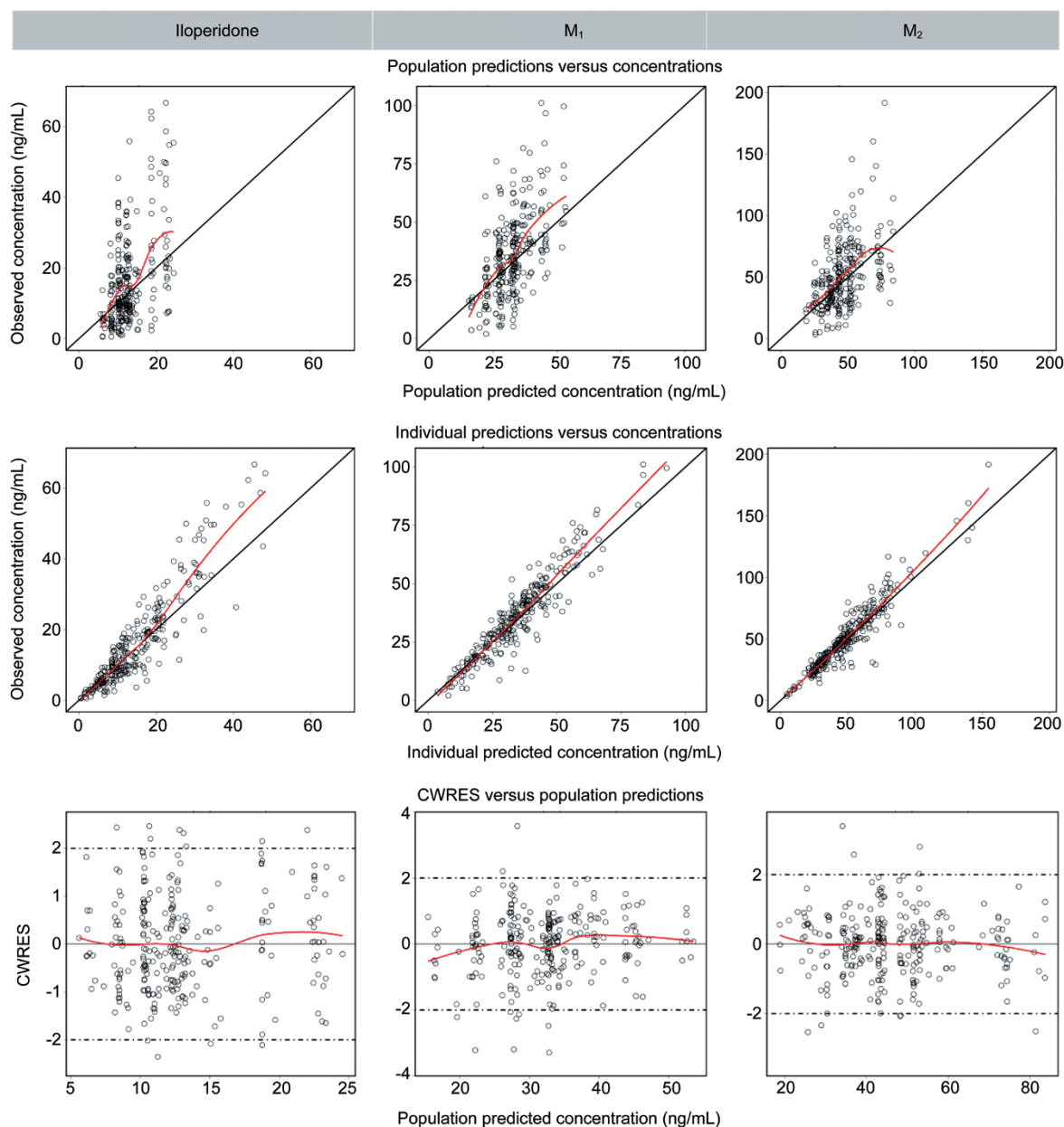


Figure 3. Goodness-of-fit plots for the final pharmacokinetic model of iloperidone, M_1 , and M_2 . Population observed versus predicted plasma (upper panel), individual observed versus predicted plasma (middle panel), CWRES (conditional weighted residuals) versus population predicted plasma (lower panel) with line of identity (black line) and regression line (red line).

affected by the *CYP2D6*10* genotypes ($P < 0.01$, Figure 5).

Discussion

In the present study, the genotypic frequencies of *CYP2D6*10* C/C, C/T, and T/T were found to be 0.16, 0.6, and 0.24, respectively, in Chinese patients with schizophrenia. These allele frequencies are similar to those that have been reported in other Asian populations but higher than those reported for Caucasians and African Americans, in whom the frequency of the *CYP2D6*10* allele was found to be 2%–5%^[9,10].

In Japanese psychiatric patients, the number of *CYP2D6*10*

alleles has been found to significantly affect dose-corrected plasma risperidone levels^[18]. Several PPK models have been developed for risperidone to study the influence of *CYP2D6*10* genotype on the pharmacokinetics of risperidone^[12–14, 21, 22]. In the current study, the influences of *CYP2D6*10* alleles on the dose-corrected plasma concentrations of iloperidone and its metabolites were evaluated in Chinese patients with schizophrenia. Although some differences were observed between the significances of M_1 and M_2 at different time points (particularly in the C_{28-4}/D and C_{28-12}/D ratio), which may have been due to the limited sample size, patients with the

Table 3. Population pharmacokinetic parameters of iloperidone and metabolites in Chinese patients with schizophrenia and bootstrap validation.

Parameters	Final model		Bootstrap	
	Estimate	RSE (%)	Median	95% CI
K_a (h^{-1})	2.26	FIX		
K_{20} (h^{-1})	0.067	13.3	0.068	0.051–0.082
K_{30} (h^{-1})	0.160	30.6	0.161	0.101–0.223
K_{40} (h^{-1})	0.106	29.6	0.108	0.057–0.173
V_2 (L)	679	13.4	668	495–979
V_3 (L)	10	FIX		
V_4 (L)	10	FIX		
K_{23} (h^{-1})	0.00451	27.7	0.00459	0.00276–0.00627
K_{24} (h^{-1})	0.00649	31.1	0.00664	0.00292–0.0113
CYP2D6*10 C/T on K_{24}	0.693	18.9	0.699	0.518–0.919
CYP2D6*10 T/T on K_{24}	0.492	24.2	0.488	0.362–0.652
CYP2D6*10 T/T on K_{23}	1.34	12.4	1.33	1.15–1.55
Inter-individual variability				
K_{20} (%)	19.5	34	19.1	6.7–29.8
V_2 (%)	35.8	19	35.0	25.6–45.6
K_{23} (%)	19.6	26	19.3	8.5–28.1
K_{24} (%)	40.9	13	39.2	30.5–48.2
Inter-occasion variability				
K_{20}	27.3	10	26.9	17.1–37.5
Residual variability				
CV^1 (%)	37.7	15	37.8	32.8–42.6
CV^2 (%)	23.6	9	23.5	19.1–29.0
CV^3 (%)	22.1	7	22.3	17.2–26.5

RSE, relative standard error; CV, proportional residual variance; CI, confidence interval; ¹ for iloperidone; ² for metabolite M_1 ; ³ for metabolite M_2 .

CYP2D6*10 T/T genotype were generally observed to exhibit a higher steady-state plasma concentration of M_1 and a lower steady-state plasma concentration of M_2 relative to the other genotype groups at all of the time points. Therefore, the CYP2D6*10 genotypes affected the steady-state concentrations of iloperidone and its metabolites, which is consistent with the fact that M_2 is primarily formed by CYP2D6^[19,20].

In this study, we developed the first parent-metabolite PPK model to evaluate the influence of the CYP2D6*10 genotype on iloperidone and its metabolites in Chinese patients with schizophrenia. Only limited samples were collected, particularly in the absorption phase, during clinical practice. A one-compartment model with first-order adsorption and elimination was able to simultaneously describe the clinical observations of the concentrations of iloperidone and its two metabolites. The absorption rate constant K_a was estimated to be $2.26 h^{-1}$ with a relatively large RSE. However, to the best of our knowledge, no K_a value has yet been reported in the literature due to limited research on iloperidone pharmacokinetics. A drug concentration-time curve from the only available pharmacokinetic study of iloperidone in Chinese healthy volunteers^[23] was generated using the Getdata Graph Digitizer (<http://www.getdata-graph-digitizer.com>) and further analyzed using a two-compartment model. This model produced

a K_a of $1.68 h^{-1}$, which is comparable to the K_a value ($2.26 h^{-1}$) estimated in our study.

Iloperidone elimination was found to be significantly affected by the CYP2D6*10 variants. Iloperidone was transformed less into metabolite M_2 and more into metabolite M_1 in patients with the CYP2D6*10 T alleles. The box plot in Figure 5 illustrates the influence of CYP2D6*10 on the clearance of iloperidone and the PPK parameters (K_{23} and K_{24}). Although the clearance of iloperidone was not significantly affected by the different CYP2D6*10 genotypes, the K_{23} and K_{24} values were notably affected by the CYP2D6*10 genotype ($P < 0.01$). The concentrations of the M_1 metabolite were higher in patients with the CYP2D6*10 T/T genotype than in patients with the CYP2D6*10 C/C or C/T genotypes, which indicated that iloperidone is primarily metabolized to M_1 in patients with the CYP2D6*10 T/T genotype. M_1 may contribute to an enhanced clinical profile and tolerability of iloperidone based on observations from a preclinical pharmacokinetic study^[6]. Clinically, compared to metabolite M_2 , metabolite M_1 is more active in terms of binding to the dopamine and serotonin receptors through the blood brain barrier. Therefore, it will be useful to apply genotype-based dosing as more therapeutic information about M_1 becomes available.

The influence of low percentages below the quantification

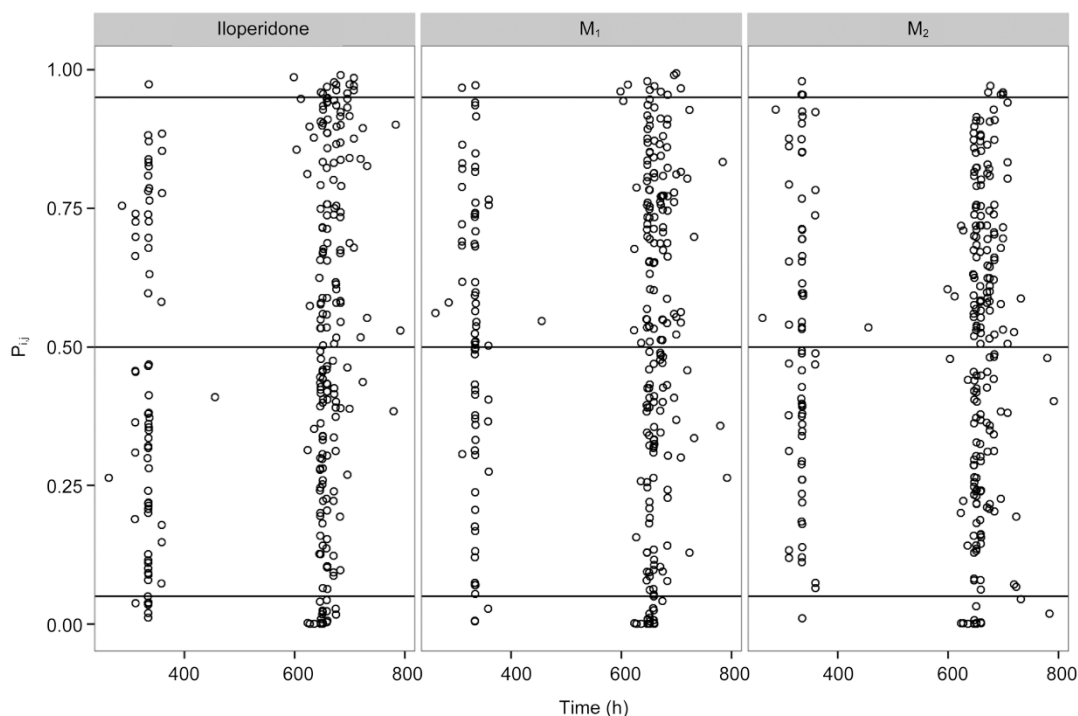


Figure 4. SVPC (Standard Visual Predictive Check) plots for iloperidone, M_1 , and M_2 . Open circles, calculated P_{ij} for each observation versus time; dashed line, model-predicted 5th, 50th, and 95th percentiles of model-predicted P_{ij} (from bottom to top). P_{ij} , percentile of each observation of each participant in the marginal distribution of model-simulated endpoints.

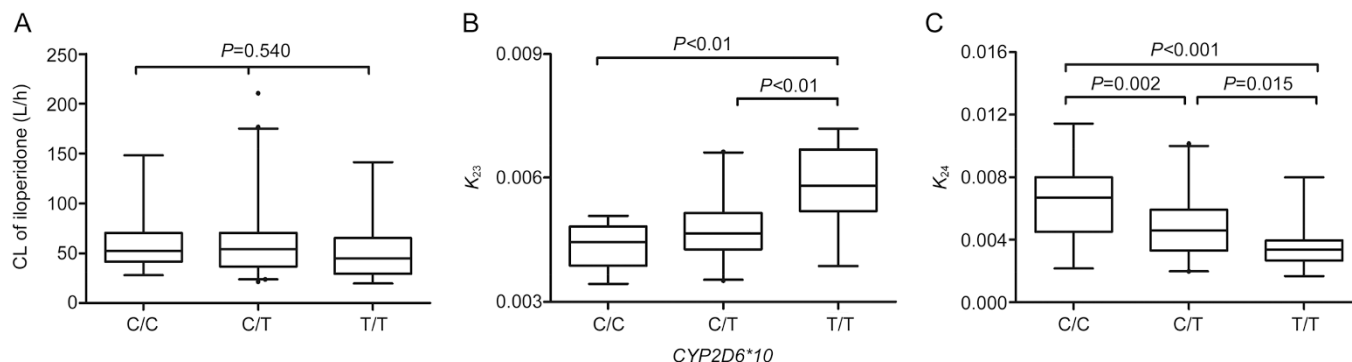


Figure 5. Box-plot of clearance (CL) of iloperidone and PPK parameters K_{23} (M_1), K_{24} (M_2) versus $CYP2D6*10$ genotypes. (A) CL of iloperidone vs $CYP2D6*10$ genotypes; (B) K_{23} vs $CYP2D6*10$ genotypes; (C) K_{24} vs $CYP2D6*10$ genotypes. The lower and upper edge of the box plot represents the first quartile and the third quartile. The whisker is 5 to 95 percentile. Solid circles indicate outliers.

limit (BQL, *ie*, $\leq 10\%$) has been demonstrated to be negligible in one-compartment models^[25]. In the current study, the percentages of BQL data for iloperidone, M_1 , and M_2 were 1.48% (4 out of 270), 0.74% (2 out of 270), and 0 (0 out of 270), respectively. Therefore, the results of the model were likely not significantly influenced by exclusion of the BQL data from the analysis.

However, the present study has some limitations. The sparse sampling design, limited number of blood samples in the absorption phase, and relatively low number of patients may have affected the estimations of the inter-individual vari-

abilities of the parameters. In the current study, the RBC value was excluded from the final model, although its influence on the distribution of iloperidone may not be negligible because the number of RBCs can affect the hematocrit value (*ie*, the primary determinant of the blood viscosity) and hence the drug plasma protein-binding rate^[24].

In our preliminary exercise, the two-compartment model provided the best fit to the mean concentration-time data for iloperidone in healthy Chinese volunteers^[23]. In contrast, a one-compartment model better described the concentration-time profiles of iloperidone and its two metabolites in Chinese

schizophrenia patients in the present study. If iloperidone in patients also exhibits the characteristics of a two-compartment model, the use of a one-compartment model to fit the data from patients in the present study would have a certain influence on the parameter estimates.

There is a lack of information in the literature related to the metabolism of iloperidone, including the exact fractions of the conversion of iloperidone to its two metabolites. Specifically, the pharmacokinetic data for iloperidone and metabolites have not been verified in Chinese patients. The details of other enzymes and other CYP2D6 alleles (*CYP2D6*2,*17*) that may play roles in the metabolism of iloperidone are not available for the current study. There are no data regarding iloperidone and its metabolites from patients who are co-medicated with CYP2D6 inhibitors. Therefore, further studies with comprehensive protocols should be performed.

In conclusion, this is the first study to identify the effects of *CYP2D6*10* variants on the PKs of iloperidone and its metabolites in Chinese patients with schizophrenia using a parent-metabolite PPK analysis. Dosages may need to be optimized for patients with *CYP2D6*10* mutations, particularly those with the *CYP2D6*10* T/T genotype.

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Author contribution

Guo-ping YANG, Shi-kun LIU, and Qi PEI conceived and designed the experiments; Jing-kai GU, and Hong-yi TAN analyzed the plasma concentrations. Cheng-xian GUO provided the sequencing data. Lu HUANG, Jie HUANG, and Yun KUANG analyzed the data. Qi PEI, Jun-jie DING, and Xiao-cong ZUO constructed the model. Lu HUANG, Qi PEI, and Guo-ping YANG wrote the paper. Guo-ping YANG, Qi PEI, Lu HUANG, Jie HUANG, Shi-kun LIU, and Xiao-cong ZUO reviewed and edited the manuscript. All authors have read and approved the manuscript.

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