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Population Pharmacokinetic Analysis Of Risperidone And Its Metabolite And Evaluation Of Effect Of Covariates On Pk Parameters

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ABSTRACT

AIMS

To characterize pharmacokinetic (PK) variability of risperidone and 9-OH risperidone using sparse sampling and to evaluate the effect of covariates on PK parameters.

METHODS

PK analysis used plasma samples collected from the Clinical Anti-psychotic Trials of Intervention Effectiveness. A nonlinear mixed-effects model was developed using NONMEM to describe simultaneously the risperidone and 9-OH risperidone concentration–time profile. Covariate effects on risperidone and 9-OH risperidone PK parameters were assessed, including age, weight, sex, smoking status, race and concomitant medications.

RESULTS

PK samples comprised risperidone and 9-OH risperidone concentrations from 20 subjects that were available for analysis. Ages ranged from 18 to 93 years. Population PK sub models for both risperidone and 9-OH risperidone with first-order absorption were selected to describe the concentration–time profile of risperidone and 9-OH risperidone. A mixture model was incorporated with risperidone clearance (CL) separately estimated for three subpopulations [poor metabolizer (PM), extensive metabolizer (EM) and intermediate metabolizer (IM)]. Age significantly affected 9-OH risperidone clearance. Population parameter estimates for CL in PM, IM and EM were 12.9, 36 and 65.4 l h-1 and parameter estimates for risperidone half-life in PM, IM and EM were 25, 8.5 and 4.7 h, respectively.

CONCLUSIONS

A one-compartment mixture model with first-order absorption adequately described the risperidone and 9-OH risperidone concentrations. Age was identified as a significant covariate on 9-OH risperidone clearance in this study.

INTRODUCTION

The atypical antipsychotics represent the first class of medications with significant advantages over previously developed neuroleptics. Large interindividual pharmacokinetic (PK) variability for antipsychotic drugs is commonly observed in routine therapeutic drug monitoring. This represents a significant clinical challenge in the treatment of psychiatric illness. An adequate understanding

of the effects of a drug is contingent upon the characterization of PK data. Clinical studies suggest that plasma levels of risperidone correlate with adverse drug effects [1]. Thus, understanding the variability in drug exposure under typical treatment conditions is important for clinical effectiveness studies.

Risperidone is an atypical antipsychotic with selective antagonistic properties at serotonin 5-HT_2 and dopamine D_2 receptors [2, 3]. Some studies have suggested that risperidone is effective in the treatment of both positive and negative symptoms of schizophrenia and has fewer adverse drug effects compared with classic antipsychotics [2].

Many factors may influence risperidone plasma concentrations, such as age and renal function. Aichhorn [4] demonstrated that the concentration dose ratio was increased by 34.8% per decade in patients >42 years old, although specific PK parameters were not assessed. Another study found that the half-life and area under the curve (AUC) of risperidone were increased in those with renal impairment compared with healthy subjects [5].

CYP2D6 polymorphisms may potentially have an impact on risperidone PK, as risperidone is primarily metabolized by CYP2D6 and to a lesser extent by CYP3A4. The formation of its major active metabolites, 9-hydroxyrisperidone (9-OH-RISP) is predominantly due to CYP2D6 [6, 7]. Drugs altering CYP2D6 or CYP3A4 activities may interact with risperidone [8].

Wang et al., [9] conducted a population PK analysis in CF1 mice to evaluate the drug–drug interactions between risperidone and CYP2D6 inhibitors (bupropion and sertraline). The results showed that AUC and elimination half-life were increased with concomitant administration of these 2D6 inhibitors. Saito et al., [10] have reported dose-dependent interaction of paroxetine with risperidone concentrations in schizophrenic patients. Spina et al., [8] have demonstrated that the levels of the active moiety (sum of the concentrations of risperidone and 9-OH-RISP) increased by 75% in schizophrenic patients taking risperidone with fluoxetine compared with risperidone alone. Moreover, de Leon et al., [11] have reported that the CYP2D6 poor metabolizer (PM) phenotype may be associated with risperidone adverse drug reactions and discontinuation, which may be due to high concentrations of risperidone resulting from the lack of CYP2D6 enzyme activity in the PM population. Other investigators have developed a mixture model for risperidone elimination in bipolar patients receiving risperidone. The sub populations of clearance rate were described as being analogous to the unmeasured CYP2D6 metabolizer genotype/phenotype [12].

The characterization of the sources of variability in both risperidone and 9-OH risperidone using highly sparse concentration sampling has not been reported. In this study, we applied a nonlinear mixed-effect modelling approach to characterize risperidone and its metabolite PK in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials for Alzheimer's disease (AD) and schizophrenia (SZ).

The mixed-effect population PK approach permits study of the sources and correlates of variability in plasma concentrations between individuals [13]. Compared with the traditional PK methods, population PK is more suitable for analysing large-scale clinical trials, where only a few samples are available per subject.

The purpose of this study was (i) to apply a nonlinear mixed-effect modelling approach to describe simultaneously risperidone and 9-OH risperidone PK parameters using limited sampling in a large number of subjects from the CATIE clinical trials, and (ii) to evaluate the impact of covariates including age, weight, sex, race, concomitant medications and smoking status on risperidone and 9-OH risperidone PK parameters.

Pharmacokinetic analysis of risperidone and 9-hydroxyrisperidone

A novel method of quantification of analytes viz., risperidone, 9- hydroxy risperidone after dosing of 2mg risperidone (RISPIDONE–2, Torrent Pharmaceuticals Ltd., India) tablets administered as a single dose orally in twenty healthy volunteers was successfully completed. The represented chromatogram of risperidone and 9-hydroxyrisperidone in human plasma collected at 2 hours after single oral dose of 2mg risperidone. We have obtained maximum plasma concentrations of risperidone in our study for each volunteer whose average value was almost twice greater that of the average of its major metabolite measured using the newly validated assay method, viz. 9-hydroxyrisperidone.

Both the compounds of interest were quantified 24 hours after dosing of risperidone in the samples [16.48 ± 5.07 vs. 10.33 ± 1.90, (mean ± SD, ng/mL)]. Similarly, the time taken to reach maximum concentration in plasma for the parent drug was nearly one fourth of that for 9-hydroxyrisperidone [0.80 ± 0.25 vs. 4.00 ± 1.12, (h)]. The Area Under plasma concentration-time Curves (AUC) of risperidone from 0-12 hours and 0-infinity hours was 92.64 ± 27.79 and 103.93 ± 32.38 (ng. h/mL). These average values of AUC were greater for the metabolite compared to their values for its parent drug, (141.80 ± 32.41 and 191.80 ± 49.81 (ng.h/mL), respectively).

The average plasma half-lives of risperidone and 9-hydroxyrisperidone were 6.17 ± 1.76 (h) and 11.54 ± 3.11 (h) respectively. Finally, the first order elimination pharmacokinetic rate constants corresponding with the terminal part of the first order elimination rate constants associate with the terminal part of plasma concentration time curves were 0.12 ± 0.04 and 0.06 ± 0.02 (h^{-1}) respectively. The volume of distribution and total clearance of the risperidone were 2.49 ± 0.53 (L/kg) and 4.95 ± 1.36 (mL/min.kg). The 9-hydroxyrisperidone volume of distribution in the participants was 2.56 ± 0.60 (L/kg) and its total clearance was 2.67 ± 0.79 (mL/min.kg). The mean plasma concentration vs. time profiles for both analytes is shown in Figure 1. The pharmacokinetic parameters were calculated by using non-compartmental pharmacokinetic model and summarized in Table 1.

Population pharmacokinetic analysis

Pharmacokinetic of risperidone plasma concentration vs time data of risperidone and its metabolite 9-hydroxyrisperidone was well fitted simultaneously using a one compartment model followed by a two compartment model during the model development. Based on OFV, and the goodness of fit plots, a PK model with 2-compartment disposition for risperidone and 1-compartment disposition for 9-hydroxyrisperidone appeared to be adequately describing the observed data Figure 2.

Based on the model, the following parameters were estimated: Absorption rate constant (KA), Fraction of parent metabolized while absorbing from the depot compartment, central compartment volume of risperidone (V2), peripheral compartment volume for risperidone (V3), inter compartment clearance (Q), non reversible clearance of risperidone by formation of 9-hydroxyrisperidone (CLPM), clearance or risperidone by other routes (CL), volume of 9- hydroxyrisperidone was assumed to be the same as that of parent (V4=V2), and clearance of 9-hydroxyrisperidone (CLM).

The basic pharmacokinetic model was implemented by using subroutine ADVAN13 and TOL=9 in NONMEM. All the models were ran using the first order conditional estimation method with eta-epsilon interaction (FOCEI).

A specific parameter and the between subject variability of the parameter was estimated using the below equation:

Pi=Ptv*exp#(ηi)

Where 'Pi' is the individual subject parameter, 'Ptv' is the typical value of the parameter in the studied population and 'η' is the log normally distributed between subject variability, with a mean of '0' and variance of 'ω2'. The residual variability was evaluated using additive, proportional and combined error models. The combined error model appeared to be describing the data adequately. The combined error model is described as below:

Obs_{ij}= $Pred_{ij}$*(i+$\varepsilon_{prop\ ij}$) + $\varepsilon_{add\ ij}$

Where Obs_{ij} is the jth observed value in ith subject, $Pred_{ij}$ is the model predicted jth value in the ith subject, and $\varepsilon_{prop\ ij}$ and $\varepsilon_{add\ ij}$ are the proportional and additive error respectively. These represent the residual intra subject variability with mean of '0' and variance of σ2.

Covariate analysis

Since the objective was to evaluate the influence of genetic polymorphism in CYP2D6 enzyme there by on the pharmacokinetic profiles of risperidone and 9- hydroxyrisperidone, the most important covariate in this analysis was the genotype of the subjects. Out of the 20 subjects included in this study, 14 subjects were normal metabolizers and 6 subjects were poor metabolizers.

The effect of two different pharmacogenetic groups on the PK parameters like CLPM, FPM, KA and CLM was evaluated as below.

TVCLPM=THETA (6)*GENE + (THETA (9)*(1-GENE))

GENE is 1 for poor metabolizers and 0 for normal metabolizers. Where THETA (6) is the typical CLPM value of poor metabolizer population and THETA (9) is the typical CLPM value of the normal metabolizer population.

The effect of genotype on the PK parameter was considered significant if the OFV reduced by at least 3.84 from the base model.

The final model was evaluated by plots of observed and predicted individual subject concentrations, and by plots of population predicted concentrations and weighted residuals. Based on the OFV and the goodness of fit plots, a 2-compartment model was considered best for risperidone and 1-compartment model for 9- hydroxyrisperidone. The best residual error model that described the entire data was combined additive and proportional error model. A combined model of risperidone and 9-hydroxyrisperidone was considered as the base model.

Incorporation of genotype as a covariate on the fraction metabolized appeared to be significant (~ 6 point reduction in OFV from baseline). The FPM estimates indicated approximately 10% lower fraction is metabolized in mutant alleles in comparison to the wild. Similarly, addition of genotype as a covariate also appeared to be significant on rate of absorption from the depot (KA), with approximately 5 point reduction in OFV from base line. The KA appeared to be faster in mutant alleles relative to that in wild type.

Addition of genotype as the covariate on CLPM (metabolic conversion of risperidone to 9-hydroxyrisperidone) showed the highest reduction in OFV (~ 17 points), indicating the metabolic conversion of risperidone to 9- hydroxy risperidone is highly influenced by the genotype of the subject. The CLPM in mutant subjects were estimated to be approximately 30% lower than that of wild type.

Further addition of covariates, over the model incorporating CLPM appeared to be not reducing the OFV substantially, this could probably because of the lower number subjects in the study. The results of the covariate analysis are presented below Table 2. The PK parameter estimates and the between subject variability estimates are tabulated below Table 3. The goodness of fit plots for the final model for risperidone and 9-hydroxyrisperidone are presented in Figure 3 and Figure 4.

Table 1: The Mean Pharmacokinetic Parameters of Risperidone and 9 - Hydroxyrisperidone in Psychotic Human Volunteers

Parameters	Risperidone (mean ± SD)	9-Hydroxyrisperidone (mean ± SD)
C_{max} (ng/mL)	16.48 ± 5.07	10.33 ± 1.90
T_{max} (h)	0.80 ± 0.25	4.00 ± 1.12
AUC_{0-t} (ng h/mL)	92.64 ± 27.79	141.80 ± 32.41
$AUC_{0-\infty}$ (ng h/mL)	103.93 ± 32.38	191.80 ± 49.81
$T_{1/2}$ (h)	6.17 ± 1.76	11.54 ± 3.11
Kel (h^{-1})	0.12 ± 0.04	0.06 ± 0.02
Vz (L/kg)	2.49 ± 0.53	2.56 ± 0.60
CL (mL/min/Kg)	4.95 ± 1.36	2.67 ± 0.79

Table 2: Summary of Covariate Analysis

Serial Number	Model	Change in OFV	Compared with Model
1	Base Model	---	---
2	Base Model with genotype as covariate on CLPM	-17.5	1
3	Base Model with genotype as covariate on FPM	-6.165	1
4	Base Model with genotype as covariate on KA	-5.071	1
5	Model 2 + genotype as covariate on FPM	-0.029	2
6	Model 2 + genotype as covariate on KA	1.363	2

Table 3: The PK Parameter Estimates and the Between Subject Variability Estimates

Parameters	Population PK Estimates	Eta SD
CL (L/hr)	0.0014	1.40
V2 (L/hr)	78.90	0.09
KA (hr^{-1})	2.13	0.56
Q (L/hr)	12.10	---
V3 (L/hr)	115.00	---
CLPM (L/hr)	11.10	0.11
CLPM (L/hr)	15.60	---
CLM (L/hr)	10.80	0.26
FPM	0.20	0.35
Risperidone ε_{add} (ng/mL)	0.001	---
Risperidone ε_{prop} (ng/mL)	0.308	---
9-hydroxyrisperidone ε_{add} (ng/mL)	0.001	---
9-hydroxyrisperidone ε_{prop} (ng/mL)	0.158	---

Figure 1: Concentration-Time Plot of Risperidone and its Active Metabolite, 9-Hydroxyrisperidone in Human Plasma

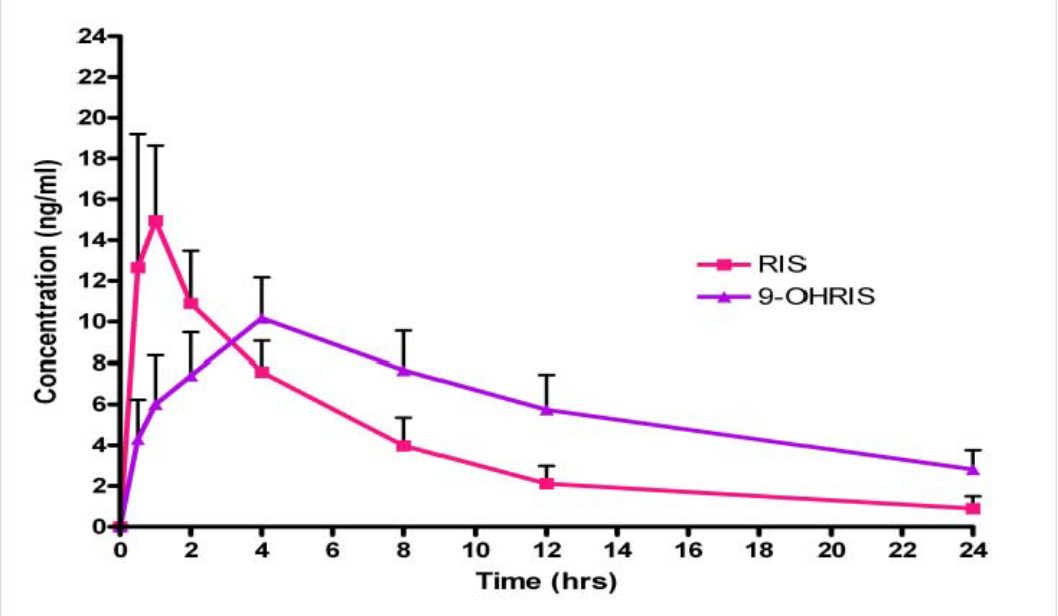


Figure 2: Scheme of the Compartment Model Describing Risperidone and 9 Hydroxyrisperidone Disposition

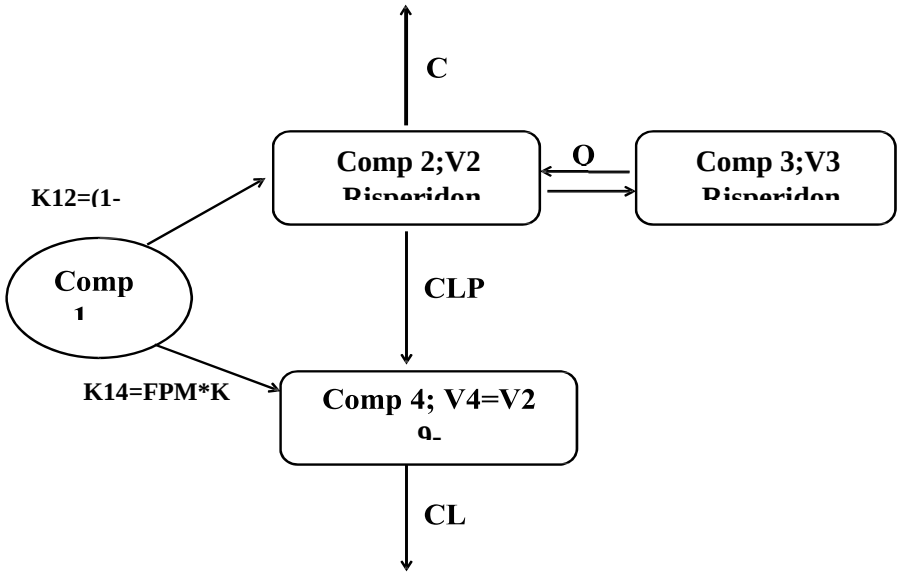


Figure 3: The Goodness of Fit Plots for the Final Model of Risperidone

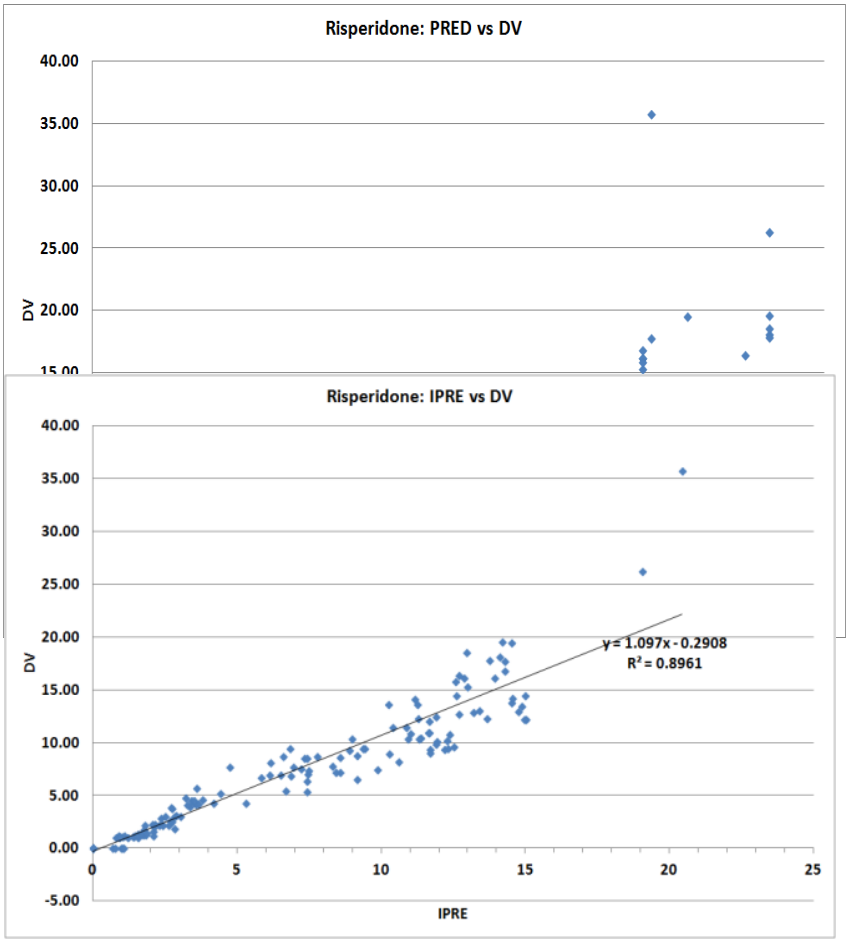
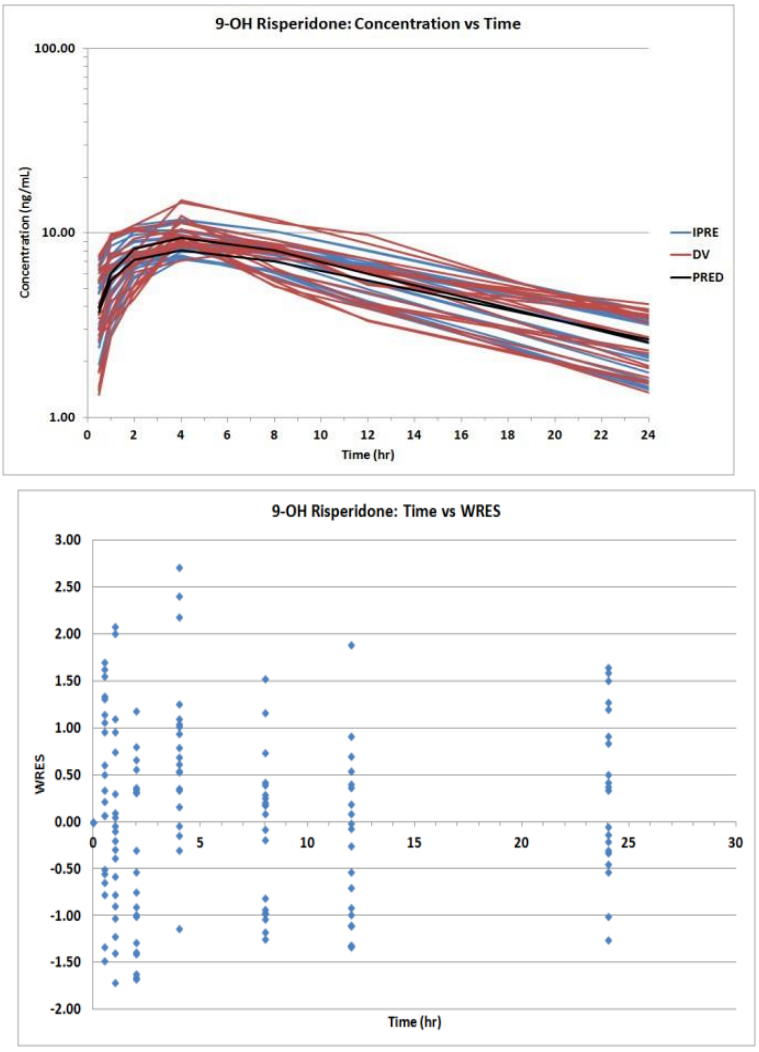


Figure 4: The Goodness of Fit Plots for the Final Model of 9 Hydroxyrisperidone (Continued)



Conclusion

In the current study, we have demonstrated significant association between the and 9-hydroxyrisperidone pharmacokinetics. Active moiety is2Yhighly predictive of the clinical response to risperidone in healthy volunteers, which is dependent on the CYP2D6*10 genotype status.

Additionally, we demonstrated that using NONMEM and multi-compartment 2Ymixed effect modelling of the population pharmacokinetics of risperidone and its metabolite, genotype has a major influence on determining the plasma concentrations of both risperidone and 9-hydroxyrisperidone. The pharmacogenetic variations in clearance of the risperidone and 9-hydroxyrisperidone may be due to differential expressions of CYP2D6 in intestinal epithelium in different genotypes of CYP2D6 * 10 allele.

Further, this could be applied to clinical decision making such as determination of dosing intervals. We recommend that the dose of risperidone in slow metabolizers must be less that used in normal metabolizers, though it has to be confirmed in further studies in our population.

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