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Population Pharmacokinetics of Risperidone in Patients with Acute Schizophrenia

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Objectives

Atypical antipsychotic agent risperidone (RISP) undergoes extensive CYP2D6 and CYP3A4 catalyzed hydroxylation to active 9-hydroxyrisperidone enantiomers (9-OH-RISP), which are predominant risperidone metabolites [1]. After oral application risperidone is almost completely absorbed, however, due to first pass metabolism to 9-OH-RISP the bioavailability is 65% [2]. Large interindividual variability in the formation rate of 9-OH-RISP has already been associated with poor, intermediate, and extensive CYP2D6 metabolizers [2,3], while the stereoselectivity of this metabolic reaction has not been thoroughly investigated *in vivo*.

In this study, the population pharmacokinetic model of RISP metabolism to 9-OH-RISP enantiomers was developed to evaluate the influence of *CYP2D6* genetic polymorphism on RISP first-pass metabolism and formation clearances of the 9-OH-RISP enantiomers.

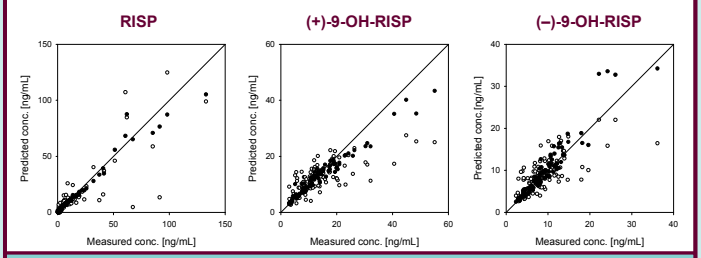
Patients and study design

This study included 50 patients (aged 18-58 years, weighted 51-102 kg) with DSM IV classification of schizophrenia or schizoaffective disorders who were initiated with oral risperidone monotherapy upon admission. Risperidone was administered either once (12 patients) or twice daily (38 patients). On day 8 after the application of the first dose two blood samples were drawn. The first blood sample was taken 2h after the last risperidone administration while the second was taken at 10 hours (twice daily regimen) or 24 hours postdose (once daily regimen). Risperidone, (+)-9-OH-RISP, and (–)-9-OH-RISP plasma concentrations were measured using validated HPLC method with electrochemical detection. The assay limit of detection was 0.50 ng/mL for all three analytes. Patients were *CYP2D6* genotyped.

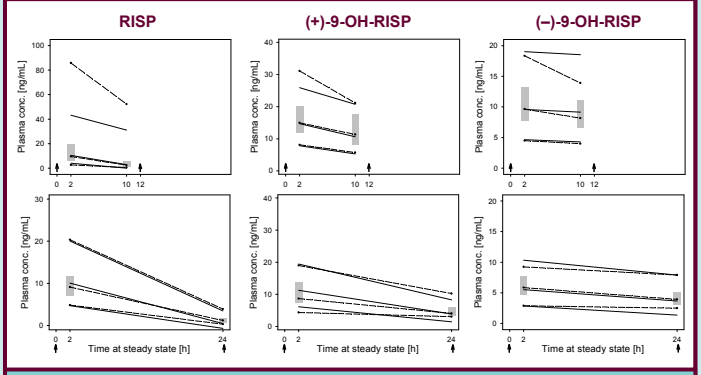
Pharmacokinetic analysis

Population pharmacokinetic (PK) analysis was performed using NONMEM (Version V, level 1.1, GloboMax LLC, Ellicott City, MD, USA) and Visual-NM (Version V, R.D.P.P., Montpellier, France), a Windows based interface to NONMEM. First-order conditional method with interaction (FOCEI) and ADVAN6 (TOL=5) subroutine were applied for parameters estimation. Exponential model was evaluated to describe the interindividual variability of the PK parameters, while for the residual variability of RISP and 9-OH-RISP concentrations additive, proportional,I and combination error models were compared.

Diagnostic plots and VPC of the final model.



Population predicted values (open circles) and individual predicted values (closed circles).



Visual predictive checks for twice (upper plots) and once (bottom plots) daily regimens. Arrows indicate risperidone administration. Dashed and solid lines correspond to median, 10%, and 90% percentiles of the measured and simulated data (1000 data sets), respectively. Gray squares represent interquartile range of the measured data.

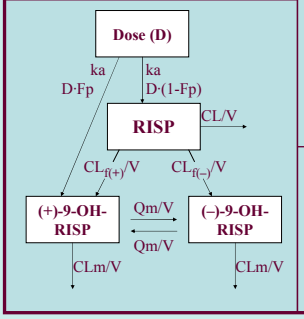
Modelling strategy aimed at a model with minimal structural and variability parameters needed to adequately describe the data. The model adequacy was evaluated by standard diagnostic plots and visual predictive checks. Additional criteria were convergence of minimization, successful covariance step, and gradients in the final iteration in the range between 10^{-3} and 10^{2}. Alternative models were compared by the likelihood ratio test. Criterion for selection of a model was a change in minimum value of objective function (ΔOBJ) of at least 3.84 per one additional parameter, corresponding to $p < 0.05$.

In the first step, base model was derived, while in the second step covariates were included into the base model one at a time and their effect was evaluated using the likelihood ratio test. Other diagnostic criteria for inclusion of covariate were reduction of interindividual variability and closer association between the observed and model predicted concentrations. Significant covariates according to the likelihood ratio test were rank-ordered and introduced into the full model. The final model was determined by backward elimination of covariates one by one from the full model to see if they should remain using a likelihood ratio test.

Results

The data were best desribed by the PK model depictured. Neglecting the chiral conversion between 9-OH-RISP enantiomers in the PK model resulted in significant increase of objective function value ($p<0.001$). Moreover, the formation of (–)-9-OH-RISP from RISP was found negligible ($CL_{f(-)} \sim 0$), suggesting that the (–) enantiomere was predominantly formed from the (+) enantiomere.

Risperidone PK model structure



$$V[L] = 1.73 \cdot WT[kg]$$

$$CL[L/h] = 0.210 \cdot (WT[kg]/70)^{0.75} \cdot (GFR[L/h]/100)^{5.08}$$

$$CL_{f(+)}[L/h] = 25.4 \cdot (WT[kg]/70)^{0.75} \cdot CYP2D6gen$$

$$CYP2D6gen = 0.0846^{0/0} \cdot 0.250^{0/x} \cdot 0.616^{0/1} \cdot 1.08^{1/x} \cdot 1.25^{XN}$$

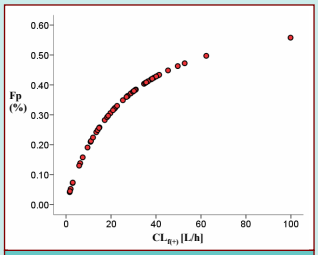
$$CLm[L/h] = 25.6 \cdot (WT[kg]/70)^{0.75} \cdot 0.635^{MI}$$

$$CL_{f(-)} \approx 0$$

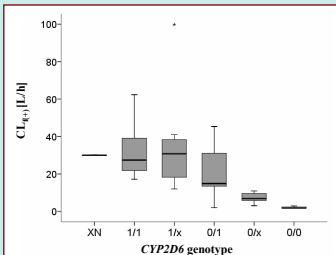
ka; absorption rate constant (fixed to 2.34) [3]
Fp; first pass metabolism
V; volume of distribution (set equal for all 3 compounds) [3]
CL; risperidone plasma clearance outside the system
$CL_{f(-)}$; (–)-9-OH-RISP formation clearance
$CL_{f(+)}$; (+)-9-OH-RISP formation clearance
Qm; interconversion clearance of 9-OH-RISP enantiomers [4]
CLm; irreversible plasma clearance of 9-OH-RISP (set equal for (+) and (–) form)

Due to specific pharmacokinetic properties of risperidone, the interindividual variability in risperidone first pass metabolism could be estimated by taking into account its relationship with the individual estimate of $CL_{f(+)}$ and its population mean value ($\theta_{CLf(+)}$):

$$Fp = (1 - TV_F) \cdot 2 \frac{CL_{f(+)}}{\theta_{CL_{f(+)}} + CL_{f(+)}} \quad \text{typical value (TV) of } F \approx 0.65\,[2], \quad TV_{Fp} = 1 - TV_F \approx 0.35$$



Relationship between risperidone first pass metabolism (Fp) and (+)-9-OH-RISP formation clearance ($CL_{f(+)}$).



Influence of *CYP2D6* genotype on (+)-9-OH-RISP formation clearance.

The investigated covariates were patients' body weight (**WT**), ***CYP2D6* genotype**, glomerular filtration rate (**GFR**), concomitant drug treatment (midazolam – **MI**), cigarette smoking (**TOB**) and **age**. Patients were combined into 6 groups according to the *CYP2D6* genotype: **0/0** (n=3), **0/x** (n=6), **0/1** (n=9), **1/x** (n=9), **XN** (n=2), and **1/1** (n=21). Nonfunctional allele, allele for diminished activity, fully functional allele, and duplications of functional alleles are marked as 0, x, 1, and XN, respectively.

FINAL MODEL PARAMETERS	Estimated value [95% CI]	% IIV (RSE)
V [L/kg]	1.73 [1.43 – 2.03]	33.2 (58)
CL [L/h]	0.21 [-1.15 – 1.56]	~ 0
effect of GFR on CL	5.08 [-9.86 – 20.0]	/
$CL_{f(+)}$ [L/h] for *CYP2D6* 1/1	25.4 [16.9 – 33.9]	55.1 (46)
effect of CYP2D6 genotype relative to 1/1:		
0/0 [%]	8.46 [4.50 – 12.4]	/
0/x [%]	25.0 [13.7 – 36.3]	/
0/1 [%]	61.6 [24.2 – 99.0]	/
1/x [%]	108 [55.0 – 161]	/
XN [%]	125 [93.2 – 157]	/
CLm [L/h]	7.77 [6.87 – 8.67]	33.0 (21)
effect of midazolam on CLm [%]	63.5 [46.2 – 80.9]	/
Qm [L/h]	25.6 [17.1 – 34.1]	~ 0
Residual error		
σ_1 [ng/mL] for RISP	0.733 [0.86 – 1.38]	
σ_2 [%CV] for RISP and 9-OH-RISP enantiomers	17.9 [11.9 – 23.9]	

Conclusions

This model demonstrates that *in vivo* formation of 9-OH-RISP from RISP is stereoselective. The main metabolite of RISP is (+)-9-OH-RISP. Formation of (+)-9-OH-RISP depends on CYP2D6 activity, while (–)-9-OH-RISP is mainly formed by chiral inversion of the (+) enantiomer.

References

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