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 the first pass metabolism is absorbed, however, due to first pass metabolism to 9-OH-RISP the bioavailability is 65% [9]. 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 diagnosis. 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, Glocomax LLC, Elliott City, MD, USA) and Visual-NM (Version V, R.P.D.P., Montpellier, France), a Windows based interface to NONMEM. First-order conditional method with interaction (FOCEI) and ADVAN1 (T1Q=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, and combination error models were compared.

Results

The data were best described by the PK model depicted. Neglecting the clinal 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 (CLf(-) ~ 0), suggesting that the (-) enantiomer was predominantly formed from the (+) enantiomer.

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 CLf(+), and its population mean value (CLf(+)),

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 grouped into 6 groups according to the CYP2D6 genotype: 00 (n=3), 0x (n=8), 0/1 (n=9), 1x (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.

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