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A population pharmacokinetic evaluation of the influence of *CYP2D6* genotype on risperidone metabolism in patients with acute episode of schizophrenia

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ABSTRACT

The objective of this prospective study was to characterize the metabolism of risperidone to (+)– and (–)–9-hydroxyrisperidone *in vivo* and to evaluate the influence of *CYP2D6* genotype. A population pharmacokinetic modeling approach was used to estimate the interindividual variability of the pharmacokinetic parameters in 50 hospitalized patients with acute episode of schizophrenia. *CYP2D6* genotype remarkably influenced the formation clearances of the risperidone metabolites, while creatinine clearance was related to the plasma clearance of 9-hydroxyrisperidone. *CYP2D6* genotype was also associated with the average plasma concentration of risperidone active moiety (a sum of all three active compounds). In comparison to the patients with *CYP2D6*1/*1* genotype, average steady-state plasma concentration of risperidone active moiety was 3.3- and 1.6-fold higher in poor metabolizers (both alleles nonfunctional; *CYP2D6*3* or **4*) and intermediate metabolizers (one nonfunctional allele and one allele for diminished enzyme activity; *CYP2D6*10* or **41*), respectively. Additionally, average plasma concentration of risperidone active moiety was higher in the patients with dystonia ($p = 0.0066$) and parkinsonism ($p = 0.046$). The results of this study imply the potential role of *CYP2D6* genotyping in personalizing risperidone therapy in patients with schizophrenia to reduce the incidence of adverse extrapyramidal symptoms.

1. Introduction

Risperidone is an atypical antipsychotic drug with strong binding affinity for serotonergic 5-HT_{2a} and 5-HT_7, and dopaminergic D_2 receptors. It is effective in treatment of schizophrenia and acute bipolar mania (Mauri et al., 2007). In human, risperidone undergoes extensive alicyclic hydroxylation at position 9, which gives rise to (+)– and (–)–9-hydroxyrisperidone enantiomers with antipsychotic activity (Megens et al., 1994; Yasui-Furukori et al., 2001). Moreover, racemic 9-hydroxyrisperidone has been introduced as a new antipsychotic agent—paliperidone (Yang and Plosker, 2007). Other risperidone metabolic pathways include hydroxylation at position 7 and oxidative N-dealkylation leading to formation of inactive metabolites (Mannens et al., 1993). 9-hydroxyrisperidone is predominantly excreted unchanged in urine (59%), the minor route of its elimination is oxidative N-dealkylation in the liver (Vermeir et al., 2008). The role of cytochrome P450 (CYP) 2D6 and 3A4 enzymes in risperidone metabolism has been thoroughly investigated. Both of these two enzymes were found to be involved in the 9-hydroxylation of risperidone *in vitro* (Fang et al., 1999; Yasui-Furukori et al., 2001). Additionally, it has been postulated that the formation of 9-hydroxyrisperidone is stereoselective, revealing that CYP2D6 might have a predominant role in formation of major (+)–9-hydroxyrisperidone metabolite, while CYP3A4 might be involved in formation of minor (–)–9-hydroxyrisperidone metabolite (Yasui-Furukori et al., 2001). However, this assumption was later questioned by the same authors in another *in vivo* study (Yasui-Furukori et al., 2003).

Large interindividual variability in risperidone plasma levels that was found in early studies was associated with poor (PM), intermediate (IM), extensive (EM), and ultra rapid (UM) CYP2D6 metabolizers (Heykants et al., 1994; Huang et al., 1993). Later studies confirmed significant influence of *CYP2D6* genotype on risperidone vs. 9-hydroxyrisperidone plasma concentration ratio (de Leon et al., 2007; Hendset et al., 2009; Llerena et al., 2004; Mihara et al., 2003; Ono et al., 2002; Riedel et al., 2005; Roh et al., 2001; Scordo et al., 1999; Wang et al., 2007). Since risperidone and 9-hydroxyrisperidone have similar pharmacologic profile and

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potency, a sum of risperidone and 9-hydroxyrisperidone plasma concentrations, referred to as the risperidone active moiety, has been considered to be of clinical relevance in risperidone treatment (Heykants et al., 1994; Huang et al., 1993). However, many studies found no significant influence of *CYP2D6* genetic polymorphism on plasma concentration of risperidone active moiety, concluding that *CYP2D6* genotype might have only limited clinical importance (Mihara et al., 2003; Ono et al., 2002; Riedel et al., 2005; Roh et al., 2001; Scordo et al., 1999; Vermeulen et al., 2007; Wang et al., 2007). Additionally, interindividual variations in risperidone and 9-hydroxyrisperidone plasma concentrations were associated with renal and liver impairment (Snoeck et al., 1995), age (Aichhorn et al., 2005; Balant-Gorgia et al., 1999; Feng et al., 2008; Snoeck et al., 1995), body weight (Balant-Gorgia et al., 1999), and co-treatment with the drugs that interfere with risperidone metabolism mostly by altering CYP2D6 or CYP3A4 activity (Balant-Gorgia et al., 1999; de Leon et al., 2007; Kim et al., 2008; Odou et al., 2000; Ono et al., 2002; Spina et al., 2000; Vermeulen et al., 2007). In this view, carbamazepine was found to significantly reduce both risperidone and 9-hydroxyrisperidone plasma concentrations (Ono et al., 2002; Spina et al., 2000; Vermeulen et al., 2007).

Pharmacokinetic (PK) properties of risperidone and 9-hydroxyrisperidone were also investigated by means of population PK modeling using mixture models (Feng et al., 2008; Vermeulen et al., 2007). This way typical risperidone plasma clearance in three subpopulations was estimated, allowing implicit determination of each patient's CYP2D6 phenotype. So far, a population PK model incorporating the effect of *CYP2D6* genotype on risperidone metabolism has not been developed. Additional factor influencing risperidone plasma clearance was concomitant medication with carbamazepine (Vermeulen et al., 2007), while 9-hydroxyrisperidone plasma clearance changed with patient age (Feng et al., 2008).

Lack of significant correlation between risperidone and 9-hydroxyrisperidone plasma concentrations with the degree of clinical improvement was noted (Spina et al., 2001). However, most recently it has been suggested that plasma concentrations are associated with improved scores (Yasui-Furukori et al., 2010). Additionally, higher plasma concentrations of risperidone active moiety were associated with higher incidence of adverse effects (Yasui-Furukori et al., 2010; Yoshimura et al., 2001). Moreover, in contrast to other atypical antipsychotic drugs, high doses of risperidone (6–16 mg/day) were related to higher risk of adverse extrapyramidal symptoms (EPS), comparable to many classical antipsychotics (Simpson and Lindenmayer, 1997).

In order to simultaneously describe the pharmacokinetic properties of all three active compounds namely; risperidone, (+)– and (–)–9-hydroxyrisperidone enantiomers, a population PK model was developed. With this model we aimed to evaluate the effect of various factors on metabolism of risperidone to 9-hydroxyrisperidone enantiomers, including patients' *CYP2D6* genotype, body weight, age, renal function, and drug co-administration. Furthermore, the scope of the present study was to use the developed population PK model to estimate risperidone exposure and to establish its relationship with the incidence of EPS in patients with acute episode of schizophrenia. In this manner, the clinical importance of genetic polymorphism of *CYP2D6* could be evaluated.

2. Methods

2.1. Patients and study design

All patients admitted to the Department of Psychiatry, University Clinical Centre Maribor in the period between January 2005 and April 2007 with DSM IV classification of schizophrenia or schizoaffective disorders, to whom risperidone was prescribed upon admission, were invited to participate in the study. Patients with medical history of dependence of psychoactive substances or abuse and patients with hepatic or renal impairment were excluded from the study. Patients receiving long-acting risperidone or other depot antipsychotics in the last four weeks, as well as patients receiving other antipsychotics in the last two weeks prior to the initiation of risperidone therapy were also excluded. The patients were treated with risperidone as mono antipsychotic therapy for at least eight days. As the risperidone dose for the majority of the patients was titrated, the exact dosing scheme for individual patient was recorded. A special attention was made on confirming patients' compliance. All concomitant medication was also documented.

On day 8 after the application of the first dose, two 10 ml blood samples were drawn. The first blood sample was taken 2 h after the last risperidone administration (approximating peak plasma concentration) while the second was taken at 10 and 24 h post-dose in patients on twice and once daily dosage regimen, respectively. The patients were examined on day 8 by two experienced psychiatrists and extrapyramidal symptoms were evaluated. Dystonia was measured with the Abnormal Involuntary Movement Scale (AIMS), akathisia with the Barnes Akathisia Rating Scale (BARS), and parkinsonism with the Simpson Angus Scale (SAS). Subsequently, EPS were described by three parameters: (i) parkinsonism, present if the patient had a mean SAS score of 0.4 or more; (ii) dystonia, present if according to AIMS at least "moderate" movements in one or more of the seven body areas, or at least "mild" movements in two or more areas were observed; and (iii) akathisia, present if according to BARS the patient was scored as "mild" or worse on the global clinical assessment of akathisia item.

Serum creatinine concentration was also measured on the same day. Creatinine clearance (CLcr) was estimated on the basis of Cockcroft and Gault formula for patients with body weight below 130% of their ideal body weight estimated using Devine formula (Bauer, 2001). For the overweight patients Salazar–Corcoran formula was applied for the estimation of creatinine clearance (Bauer, 2001).

Written informed consent was obtained from all the patients. The study was approved by the Slovenian Ethics Committee for Research in Medicine.

2.2. Genotyping

Genotyping was performed blind to the patient's clinical status. A 10 ml blood sample was obtained from each subject for *CYP2D6* genotyping. The salting out method using Qiagene FlexiGene kit (Qiagen, Hilden, Germany) was applied for isolation of genomic DNA from peripheral blood leukocytes (Miller et al., 1988). *CYP2D6* genotyping was performed as previously described (Kores-Plesnicar et al., 2006). In addition, *CYP2D6*41* allele was determined based on the detection of G2988A polymorphism with a custom TaqMan SNP genotyping assay (Applied Biosystems, Foster City, California, USA) (Raimundo et al., 2004). Primer and probe sets were designed as follows: Forward Primer: 5′-GAGCCCATCTGGGAAACAGT, Reverse Primer: 5′-GGTGTCCCAGCAAAGTTCATG, VIC-probe: 5′-CCTGTACCCTTTCTCCCT, FAM-probe: 5′-CTGTACCCTTCCTCCCT. Real time PCR experiment was performed on the ABI 7500 instrument (Applied Biosystems) in a 5 μl reaction mix containing 0.125 μl of TaqMan SNP genotyping assay, 2.5 μl of TaqMan Universal PCR Master Mix and 120 ng of DNA. Alleles where none of the tested polymorphisms were detected were classified as *CYP2D6*1* alleles.