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Short communication

Concomitant influence of CYP2D6 phenotype and *ABCB1* overall haplotype/genotype on pharmacokinetics of risperidone and 9-hydroxyrisperidone in healthy volunteers

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Introduction

Risperidone is a broadly prescribed antipsychotic drug and potent dopamine D2 and serotonin 5-HT2 receptors antagonist, effective in alleviation of positive and negative symptoms in schizophrenia and related psychotic disorders. Its main metabolite - 9-hydroxyrisperidone (9-H-RIS), a product of cytochrome (CYP) 2D6 enzyme activity, is equipotent to parent drug regarding dopamine receptor affinity. Cumulative concentrations of risperidone and 9-OH-RIS represent the active moiety (AM), while their ratio is referred as metabolic ratio (MR). Furthermore, risperidone and 9-OH-RIS are substrates and inhibitors of efflux transporter P-glycoprotein (multidrug resistance protein 1, MDR or ABCB1). ABCB1 is involved in the control of drug bioavailability, affecting its absorption, elimination and transport through the blood-brain barrier (Jukic et al, 2019).

Existing *CYP2D6* gene polymorphisms result in phenotypes that can be categorized as poor (PM), intermediate (IM), normal (NM) and ultra-rapid metabolizers (UM) of numerous drugs, including risperidone. PM phenotype is linked to higher risperidone exposure and subsequent higher risk of adverse effects. In UMs, lower exposure to risperidone is related to higher risk of treatment ineffectiveness. According to available studies, levels of 9-OH-RIS and AM are not affected by polymorphisms in *CYP2D6* (Dodsworth et al., 2018).

Although *ABCB1* gene is characterized by high polymorphism, investigators are primarily focused on three SNPs (Single Nucleotide Polymorphisms), 1236 C>T in exon 21 and 3435C>T in exon 26, as well as 2677G>T/A in exon 21, which may influence the PK parameters of risperidone, 9-OH-RIS and AM (Ganoci et al., 2021).

The objective of this study is to evaluate the effect of concomitant CYP2D6 phenotype and *ABCB1* overall haplotype/genotype on the pharmacokinetics (PKs) of risperidone and 9-OH-RIS in healthy volunteers.

Materials and methods

The study sample comprised of sixteen unrelated, healthy male volunteers, aged 19-49 years, with Ideal Body Weight according to the Body Mass Index 18-28, non-smokers, included into a single center, open, single dose, randomized, balanced, two - way crossover study with a wash - out period of two weeks, aimed to evaluate and compare the relative bioavailability of two Risperidone 2 mg tablets formulations, conducted at the Department of Preclinical and Clinical Toxicology and Pharmacology - Faculty of Medicine, University “Ss. Cyril and Methodius” in Skopje, R.N. Macedonia.

Concentrations of risperidone and its active metabolite were determined using validated HPLC-MS/MS method. Identification of *CYP2D6* (*2A [rs16947]; *2XN [rs1135840]; *3 [rs35742686]; *4 [rs3892097]; 6A [rs5030655]; *9 [hCV32407229]; *10A [rs1065852]; *41 [rs28371725]; CNV [Hs00010001_cn]) and *ABCB1* (C1236T [rs1128503]; G2677A/T [rs2032582]; C3435T [rs1045642]) variant alleles was completed at the Center

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for Biomolecular and Pharmaceutical analysis - Faculty of Pharmacy, Skopje, University "Ss Cyril and Methodius" in Skopje, R.N. Macedonia, using real-time polymerase chain reaction method [MxPro 3005P, Stratagene, La Jolla, CA, USA] and TaqMan SNP/drug metabolism genotyping assays according to the manufacturers' instructions [Applied Biosystems, Foster City, CA, USA].

All PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el} ,Cl_{tot}, $t_{1/2}$) expressed as mean ± SD, were estimated from the plasma concentrations-time dependent data and calculated using KINETICA™ 2000 software (Innaphase corporation, USA). The PK/PGx correlation was statistically evaluated using MedCalc 20.111 software. Differences in PKs among groups with different CYP2D6 phenotype/*ABCB1* overall haplotype/genotype were assessed using Kruskal-Wallis test and Conover test for *post hoc* analysis. Factors with $p \leq 0.05$ were considered as statistically significant.

The study was conducted in accordance with the national legislation on clinical research in humans and the Helsinki declaration.

Results and discussion

High interindividual variabilities (interval between the minimal and maximal value), regarding all PK parameters, were observed for both, risperidone and 9-OH-RIS. Variation of AUC_{0-t} and $AUC_{t-\infty}$ for risperidone was 11.22-388.32 mg h L^{-1} and 0.38-14.14 mg h L^{-1}; while it was 57.05-248.35 mg h L^{-1} and 3.59-20.28 mg h L^{-1}, respectively, for 9-OH-RIS.

Mean values of Cl_{tot}, K_{el}, c_{max}, t_{max} and $t_{1/2}$ for risperidone vs its metabolite were 0.06 L h^{-1}, 0.21 h^{-1}, 12.10 mg L^{-1}, 0.92 h and 7.95 h vs. 0.01 L h^{-1}, 0.30 h^{-1}, 7.83 mg L^{-1}, 4.20 h and 24.17 h, respectively. The calculated AM and MR were 19.93 mg L^{-1} and 3.40, respectively.

According to the results from CYP2D6 genotyping, 2 subjects were identified as PMs, 3 as UMs and 11 as NM/IM. The three *ABCB1* polymorphisms were addressed as overall haplotype/genotype, and subjects were classified as homozygote carriers of variant alleles-TT/TT/TT (N=5), homozygote carriers of wild type alleles-CC/GG/CC (N=2) and heterozygote carriers of both allele types (N=9).

In order to evaluate the concomitant influence of CYP2D6/*ABCB1* status on the PK variability, subjects were subsequently classified in seven distinctive groups: PM/variant (N=1), PM/heterozygote (N=1), UM/variant (N=1), UM/heterozygote (N=2), NM/IM/variant (N=3), NM/IM/wild (N=2) and NM/IM/heterozygote (N=6). None of the subjects was classified as PM/wild and UM/wild.

The PK/PGx statistical analysis revealed that CYP2D6/*ABCB1* status was associated with a variability in following risperidone PK parameters: AUC_{0-t} ($p=0.019$), $AUC_{t-\infty}$ ($p=0.031$), $AUC_{0-\infty}$ ($p=0.019$), Cl_{tot} ($p=0.019$), c_{max} ($p=0.035$), and t_{max} ($p=0.025$). Excluding t_{max} ($p=0.004$), no significant difference in 9-OH-RIS PKs was observed across the groups. Interindividual variability in MR, but not AM was found to be substantially related to concomitant CYP2D6/*ABCB1* status ($p=0.005$).

In general, according to the *post hoc* analysis, there was no statistical differences in PKs between CYP2D6 PMs or UMs, carriers of *ABCB1* homozygote vs. heterozygote variant alleles. On the contrary, there was a significant difference ($p<0.05$) in risperidone AUC_{0-t}, AUC_{t-inf} and Cl_{tot} between CYP2D6 NM/IMs, carriers of *ABCB1* homozygotes of variant alleles vs. wild type alleles.

The obtained results are in line with the previously published data, signifying the role of *CYP2D6* as an important genetic factor affecting the exposure to risperidone, but not to 9-OH-RIS and/or AM. Our results also validate the significance of *ABCB1* overall haplotype/genotype regarding systemic bioavailability of risperidone (Ganoci et al., 2020). Furthermore, presented data suggest a possibility for a subsequent *ABCB1* genotyping in CYP2D6 NM/IMs patients, particularly in those experiencing risperidone treatment failure.

Conclusion

In conclusion, CYP2D6 phenotype, compared to *ABCB1* overall genotype/haplotype, is the predominant genetic factor affecting PK parameters of risperidone. The justification for concomitant CYP2D6 and ABCB1 genotyping has to be additionally proven in studies with larger sample size and in prospective randomized clinical trials.

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