THE PREDICTIVE VALUE OF ABCB1, ABCG2, CYP3A4/5, AND CYP2D6 POLYMORPHISMS FOR RISPERIDONE AND ARIPIPRAZOLE PLASMA CONCENTRATIONS AND THE OCCURRENCE OF ADVERSE DRUG REACTIONS

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INTRODUCTION

In the last decade the use of antipsychotics in the pediatric population was increased in Europe. However, unanswered questions on the role of genetic factors on both efficacy and safety of antipsychotics especially in children and adolescents still exist.

AIM

To investigate the impact of the main polymorphisms occurring in CYP3A, CYP2D6, ABCB1 and ABCG2 genes on risperidone and aripiprazole plasma concentrations and their association with the occurrence of adverse drug reactions in Caucasian pediatric patients.

METHODS

Ninety pediatric patients were enrolled by three Italian neuropsychiatry departments, from March 2012 to March 2014. Blood samples were collected for pharmacogenetic analyses and patients' DNA was isolated. We selected and evaluated the functional variants mapping in CYP2D6 (*3 del/A rs35742686, *6 del/T rs5030655, *4 G>A rs3892097, rs1080985 G>C promoter variant and assay ID Hs00010001_cn gene duplication), in CYP3A (CYP3A4 *22 C>T rs35599367, CYP3A5 *3 A>G rs776746) ABCB1 (c.3435 C>T rs1045642, c.2677 C/A/T rs2032582) and ABCG2 (c.421 C>A rs2231142) genes. Linear mixed-effects models adjusted for the aforementioned genotypes, gender, age, Body Mass Index (BMI), serum creatinine, selective serotonin reuptake inhibitors (SSRIs), first-generation antipsychotics (FGAs) and antiepileptic drugs (AEDs)-use were used to assess the influence of polymorphisms on risperidone and aripiprazole plasma concentration/dose ratio (Ct/ds). Moreover a multivariate Cox regression model adjusted for gender, age, BMI, serum creatinine concentration, SSRIs-, FGAs- and AEDs-use, CYP3A, CYP2D6 phenotypes, ABCB1 and ABCG2 genotypes was used to compare the risk of developing adverse drug reactions among functional variants.

RESULTS

The observed allele frequencies of CYP2D6, CYP3A4, CYP3A5, ABCB1 and ABCG2 genes in our study population did not statistically deviate from the Hardy Weinberg equilibrium for investigated alleles, except for functional variant *6 of CYP2D6 ($p<1.2*10\text{-}6$). Patients with the CA/AA ABCG2 genotype had a statistically significant lower risperidone Ct/ds (p-value: 0.007) and an higher estimated marginal probability of developing metabolism and nutrition disorders as compared to the ABCG2 c.421 non-CA/AA genotypes (p-value:0.008). Multivariate analysis revealed that the

ABCG2 c.421 CA/AA genotype was found associated to a higher hazard (p-value: 0.004) of developing adverse drug reactions classified as metabolism and nutrition disorders. The ABCB1 2677TT/3435TT genotype had a statistically significant lower aripiprazole Ct/ds if compared with patients with others ABCB1 genotypes (p-value: 0.026). Information obtained on ABCB1 and ABCG2 gene variants may result useful to tailor treatments with these drugs in Caucasian pediatric patients.

CONCLUSION

This study shows that pediatric patients carrying the ABCG2 c.421 CA/AA genotype had statistically lower risperidone Ct/ds that resulted in a higher estimated marginal probability of developing metabolism and nutrition disorders when compared to patients with ABCG2 c.421 non-CA/AA genotypes in both crude and adjusted analyses. Patients carrying the ABCB1 (G2677T/A-C3435T) TT/TT genotype had statistically lower aripiprazole Ct/ds when compared with patients carrying others ABCB1 genotypes. The relationship between pharmacogenetic, pharmacokinetic and safety profiles of risperidone and aripiprazole, if confirmed in larger studies, it could strengthen the usefulness of combining therapeutic drug monitoring, pharmacogenetic and pharmacovigilance methods to tailor treatments with these drugs in Caucasian pediatric patients.

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