Poster

[P26-4] P26-4: Central nervous system drugs (3)

Chair: Christoph Hiemke, Germany

Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall)

[P26-4-1] Comparison of reduced function CYP2D6 alleles on venlafaxine and risperidone metabolic ratios

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Keywords: CYP2D6, venlafaxine, risperidone, metabolic ratios, reduced function alleles

Background

Reduced function CYP2D6 alleles are frequently found globally, but importance of these alleles for CYP2D6 phenotype is limited. Risperidone/9OH-risperidone and N-desmethylvenlafaxine/ O-desmethylvenlafaxine metabolic ratios (MR) are established as biomarkers of CYP2D6 phenotype. The aim of this study was to compare the impact of the CYP2D6 reduced function alleles *9, *10 and *41 on these phenotype biomarkers in a large population of mainly Caucasian origin.

Methods

Retrospective therapeutic drug monitoring data from patients with known CYP2D6 genotype and steady state serum concentrations of risperidone (RIS), venlafaxine (VEN) and respective metabolites were included. Patients were divided in 10 different genotype subgroups, representing different combinations of CYP2D6 active- (*1), reduced- (*9, *10 and *41) and null alleles (*3, *4, *5 and *6). Patients with no detected variant alleles (*1/*1, EM) constituted the reference group in the two multiple linear regression models.

Results

A total of 1044 patients were included in the study (risperidone n=429, venlafaxine n=615). Both RIS MR and VEN MR were consistently higher in carriers of *41 than *9 or *10. Heterozygous carriers of the included reduced function alleles (*1/*9, *1/*10 or *1/*41) were not different from the reference group (*1/*1, $p>0.4$). Heterozygous carriers of null alleles (*1/*4, *1/*5 or *1/6) had 2.1-fold ($P=0.002$) and 2.4-fold ($P=0.003$) higher metabolic ratios for RIS and VEN compared to *1/*1. Patients with one null allele and one *9 *or* *10 allele had 4.6-fold 5.8-fold higher RIS and VEN MR (both $P<0.001$). Patients with one null allele combined with one *41 allele had 8.6-fold and 8.7-fold higher MR of RIS and VEN (both $P<0.001$). Finally, homozygous carriers of null alleles (poor metabolizers) had a 15.8-fold and 23.0-fold higher MR for RIS and VEN compared to EM (both $P<0.001$).

Conclusions

This study shows that the reduced function allele CYP2D6*41 has a greater impact on phenotype than CYP2D6*9 and *10, at least in Caucasians. Carriers of CYP2D6*41 combined with null alleles express metabolic phenotypes close to poor metabolizers. Routine pharmacogenetic test panels should therefore include CYP2D6*41.