TARDIVE DYSKINESIA AND CYTOCHROME P450 1A2 GENE POLYMORPHISM IN RUSSIAN PATIENTS WITH SCHIZOPHRENIA


*From the Russian Federation: Tomsk Mental Health Research Institute; Institute of Chemical Biology and Basic Medicine, Novosibirsk; Chita State Medical Academy
+ From the Netherlands: Erasmus University Medical Center, Hospital Pharmacy, Rotterdam; University of Groningen, Pharmacy, Groningen

Email: gavrilivg@mail.ru

Background

Tardive dyskinesia (TD) is a potentially irreversible involuntary movement disorder with prevalence of about 20–30% in psychiatric patients on long-term treatment with antipsychotics. The identification of genetic factors contributing to development of TD would be of considerable clinical interest for individualized drug treatment. TD can be dissected into two distinct sub syndromes; orofaciolingual (TDof), involves movements of mouth and face) and limb-truncal dyskinesias (TDlt) which probably have different genetic liability [1]. Recent investigations suggest that CYP1A2 may contribute to the development of TD as another CYP which may influence typical antipsychotics metabolism acting as a low-affinity high-capacity metabolizing enzyme [2, 3].

Objective

The aim of this study was to investigate the association between orofaciolingual (TDof) and limb-truncal dyskinesias (TDlt) and Cyp1a2*1F (C-163A, rs762551) polymorphism in Russian psychiatric inpatients.

Methods

TD was assessed cross-sectionally in patients with clinically-established schizophrenia from four psychiatric centres in West Siberia by the use of the Abnormal Involuntary Movement Scale (AIMS). TDof and TDlt were assessed with AIMS items 1–4 and 5–7, respectively. Standard protocols were applied for genotyping. Analysis of covariance (ANCOVA) was used to compare the mean AIMS scores for each of the genotypic classes, with age, sex, duration of disease, chlorpromazine equivalent (CPZEQ) incorporated as covariates.

Results

In total 319 Russian Caucasians patients (196 males, 123 females) with an age of 43±15.8 years (sample mean ± SD) met the inclusion criteria. All patients had clinically-established schizophrenia and were included from four different psychiatric departments in West Siberia. Mean of disease duration was 17±14 years. The genotype distribution of Cyp1a2*1F (C-163A, rs762551) polymorphism were in agreement with Hardy–Weinberg Equilibrium (\( \chi^2 =1.09 \), p=0.7). 44.8% were homozygous for the C-allele, 44.2% were heterozygous, and 10% were homozygous for the A-allele. Analysis of covariance (ANCOVA) with age, sex, duration of disease, chlorpromazine equivalent (CPZEQ) incorporated as covariates showed that TDlt, but not TDof, is an association with Cyp1a2*1F (C-163A, rs762551) polymorphism (F=3.27, p=0.039). Patients with the C/C genotype had a higher mean AIMS items 5–7 score than those with the A/C or the A/A genotype, as it shown in the Fig. 1. Pair-wise comparison showed Mann-Whitney Test meaning between groups with genotypes AA and AC, AA and CC, AC and CC were 8774 (p=0.033), 1736 (p=0.021), 2023 (p=0.311) accordingly.

Discussion

The increased TDlt severity in patients with the (C/C) genotype for CYP1A2 observed in the current study is in agreement with the literature data [2]. It should be noted that smoking is an established inducer of CYP1A2 enzyme activity. Additionally, the plasma concentration of most typical antipsychotics is significantly reduced by smoking. It can be assumed that decrease of plasma level of typical antipsychotics in smokers are caused by activation of CYP1A2. 79% schizophrenic patients are smokers in our study and thus may have an increased CYP1A2-dependent pathway of metabolism of typical antipsychotics.

Conclusion

Although type I or II errors can not excluded, the present study suggests that the C/C homozygousisnt of rs762551 might be associated with limb-truncal but not with orofacial TD. Futher studies are needed to support our findings

References