MDR1 GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SIDE EFFECTS FOLLOWING ACUTE ANTIPSYCHOTIC TREATMENT

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Background *Multidrug resistant protein (MDR1) gene, which codes for P-glycoprotein is amongst the best understood mediators of drug resistance. It functions as an ATP dependant efflux transporter and is widely localized in normal tissues including the gastrointestinal tract, blood cells, biliary tract, kidney and brain. It plays a major role in absorption, distribution and elimination of various xenobiotics by excreting them into bile, urine and intestinal lumen. It transports drugs against a concentration gradient across the blood-brain barrier back into the plasma and thereby reduces their bioavailability in the brain. Studies using mice models reported that P-glycoprotein-deficient mice had greater drug penetration into brain than wild-type animals. Two common single nucleotide polymorphisms (SNP), a silent mutation C3435T in exon 26 and SNP G2677T in exon 21 were described in MDR1 gene. A twofold reduction in intestinal P-gp expression has been reported in homozygous carriers of the 3435 T allele in exon 26. Because most second generation antipsychotics were shown to be P-gp substrates we hypothesized that polymorphisms in MDR1 that alter P-gp function may influence individual's response to antipsychotic drugs. Differential entry of antipsychotics into the brain might explain differences in response and side effects, even if plasma concentrations do not differ.*

Aim *The present study was therefore designed to examine whether C3435T and G2677T/A polymorphisms in MDR1 are related to extrapyramidal side effects in acute antipsychotic treatment of schizophrenia.*

Methods *A genotyping approach using sequence specific PCR and TaqMan genotyping assays (Applied Biosystems) and was used to determine C3435T and G2677T/A MDR1 polymorphisms, respectively in total of 65 patients acutely treated with haloperidol or risperidone either for the first episode of schizophrenia spectrum disorders or for the psychotic episode after tapering their maintenance treatment. Extrapyramidal side effects were assessed with the Simpson-Angus Extrapyramidal Side Effects Scale (EPS), the Barnes Akathisia Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS). The Slovenian Ethics Committee for Research in Medicine approved the study.*

Results *Haloperidol was significantly more administered in patients with high BPRS and CGI baseline scores. Further, patients with high baseline BPRS and CGI scores received higher dosages of drugs. Nevertheless, haloperidol and high dosages of treatment were associated with a poor outcome in terms of final BPRS scores. A poor outcome was also associated with old age and elevated body mass index (BMI). Akathisia (BARS) was dependent on drug dosage, extrapyramidal symptoms (EPS) were more severe in patients treated with haloperidol and at a high dosage and, finally, tardive dyskinesia (AIMS) was marginally dependent on age but mostly on illness duration and it was more severe in patients treated with haloperidol and a high dosages. The frequencies of C3435T (exon 26) genotypes were: CC = 13.5 %, CT = 42.3 %, TT = 44.2 % and the frequencies of G2677T/A (exon 21) genotypes were: GG = 13.5 %, GT = 51.9 %, GA = 5.8 %, TT = 26.9 %, TA = 1.9 %. Both polymorphisms were in Hardy-Weinberg Equilibrium (HWE) (respectively p = 0.15. p = 0.55) and they were in strong Linkage disequilibrium (LD) (D' = 0.85. Chi-sq = 71.1 d.f. = 2 p <0.0001). We did not find any association between MDR1 variants and extrapyramidal side effects (BARS: MDR1ex21 p = 0.53. MDR1ex26 p = 0.42; AIMS: MDR1ex21 p = 0.22. MDR1ex26 p = 0.52; S-A ESP: MDR1ex21 p = 0.53. MDR1ex26 p = 0.91)*

Conclusion *Neither MDR1 C3435T (exon 26) nor G2677T/A (exon 21) were associated with the occurrence of EPS effect in schizophrenic patients acutely treated with antipsychotics.*