THERAPEUTIC MONITORING OF CLOZAPINE, ABCB1 GENOTYPING AND RESPONSE TO TREATMENT IN PSYCHOTIC PATIENTS

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Background and Aim. Clozapine, an atypical antipsychotic drug, is used to treat psychotic patients who are resistant to typical antipsychotics. The drug is substrate of the transmembrane transporter ABCB1, also known as P-gp, whose activity is related to the presence of single nucleotide polymorphisms (SNPs), namely C3435T on exon 26, G2677T on exon 21 and C1236T on exon 12. The aim of the present study was to evaluate possible correlations among plasma levels of clozapine and its active metabolite norclozapine, ABCB1 haplotype and polymorphisms, and response to the drug in patients affected by schizophrenia, schizoaffective disorders and bipolar disorders with psychotic features. **Patients and Methods.** Forty-one consecutive patients, 27 men and 14 women (age, 34.5±8.0 and 49.1±14.7 years, respectively), were enrolled. A blood sample was withdrawn when clozapine achieved its steady state plasma levels, at least 14 days after the start of drug administration. Clozapine and norclozapine plasma concentrations were determined by a validated UV-HPLC method, while C3435T, G2677T and C1236T SNPs were determined by RFLP-PCR or using real-time PCR genotypization assay on a Taqman platform (Applied Biosystems). Treatment response was evaluated by using CGI scale. Results obtained from statistical analysis were expressed as mean±standard deviation values, and *P* values lower than 0.05 were considered significant. **Results**. Plasma levels of clozapine and norclozapine were 197.6±143.2 and 107.1±84.4 ng/ml, respectively. In this study, 6 patients (4 males and 2 females) experienced a negligible benefit from treatment ("minimally improved" or "no change" according to the CGI score), despite they received higher doses of the drug (196±135 mg/die) with respect to the responders ("much improved" or "very much improved" according to the CGI score) (160±104 mg/die). Noteworthy, dose-normalized plasma levels of clozapine and norclozapine were significantly higher in responder patients (1.71±1.4 and 0.75±0.46 ng/ml/mg, respectively) than in 6 nonresponders (0.83±0.53 and 0.40±0.21 ng/ml/mg, respectively), suggesting an alteration of absorption or excretion of the drug and catabolite. However, haplotypes of ABCB1, as well as the three single SNPs, failed to predict the response to clozapine in the present patients. **Conclusions.** These results demonstrate that dose-normalized plasma levels of clozapine and its metabolite predict treatment effectiveness, while further studies are warranted to investigate the role of ABCB1.