Role Of CYP1A2 Polymorphisms In Clozapine-Induced Adverse Reactions

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Abstract

Objectives: The genetically polymorphic enzyme cytochrome P450 (CYP) 1A2 contributes to the biotransformation of the antipsychotic drug clozapine (CLO). Two polymorphisms are known to affect significantly 1A2 activity: 1A2*1F which increase metabolism and 1A2*1C which decrease it. These SNPs, located in the promoter region of the gene, may be responsible of a different CYP1A2 mRNA expression and could help to explain interindividual differences in enzyme activity. Aim of these research was to evaluate the impact of these polymorphisms on CLO pharmacokinetics and on the occurrence of adverse reactions (ADRs).

Methods: All enrolled subjects were patients treated with CLO in our department during the period 2008-2009. Inclusion criteria for case-group were: diagnosis of psychotic disorder, normal liver and renal function, absence of concomitant diseases, occurrence of significant CLO-induced ADRs. Patients who assumed CYP1A2 inducer or inhibitory drugs, except smoking, were excluded. We considered significant CLO-induced ADRs all reactions which led to CLO discontinuation or a permanent dose reduction, and were related to CLO according to the clinical evaluation of the clinicians confirmed by a "certain" or "probable" result at WHO-Uppsala criteria (WHO Uppsala Monitoring Centre-UMC: http://www.who-umc.org). In the control-group we enrolled patients treated for at least 1 year with CLO without showing ADRs, with the same clinical features, matched for age, sex, CLO doses and smoking habits. Clinical parameters were correlated with the CYP1A2 genotype and allelic combinations and with CYP1A2 mRNA expression levels.

Results: The ratings for side effects, like sedation, constipation, scialorrea, were significantly higher in CYP1A2 poor metabolizers genotypes.

Conclusions: Treatment with clozapine could be dangerous in extremely slow metabolizers and ineffective in extremely rapid. Although genotyping explained only a fraction of the adverse events, it could be a good predictor of adverse events.