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PHARMACOGENETICS

CYP1A2 genotype affects carbamazepine pharmacokinetics in children with epilepsy

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Abstract
Purpose The purpose of this study is to investigate the effect of two of the most important functional *CYP1A2* variations −3860G > A and −163C > A on carbamazepine pharmacokinetics in Serbian pediatric epileptic patients.
Methods The study involved 40 Serbian pediatric epileptic patients on steady-state carbamazepine treatment. Genotyping for −3860G > A and −163C > A was carried out using PCR-RFLP method, and carbamazepine plasma concentrations were determined by high pressure liquid chromatography (HPLC) method. For pharmacokinetic analysis, NONMEM software with implementation of ADVAN 1 subroutine was used.
Results *CYP1A2* polymorphism −163C > A was found at the frequency of 65.0 %, while −3860G > A was not detected. The correlation between weight-adjusted carbamazepine dose and carbamazepine concentration after dose adjustment was significant only in carriers of −163C/C and C/A genotypes ($r = 0.68$, $p = 0.0004$). The equation that described population clearance (CL) was CL (l/h) = 0.176 + 0.0484 * SEX + 0.019 * *CYP1A2* + 0.000156 * DD, where SEX has a value of 1 if male and 0 if female, *CYP1A2* has a value of 1 if −163A/A and 0 if −163C/C or C/A, and DD is the total carbamazepine daily dose (mg/day).
Conclusions *CYP1A2* −163A/A genotype influence carbamazepine pharmacokinetics. In addition to sex and total carbamazepine daily dose, −163C > A *CYP1A2* polymorphism should be considered as a predictor of carbamazepine clearance.

Keywords *CYP1A2* genotype · Carbamazepine · Pharmacokinetics · Children

Introduction

Carbamazepine is a well-known and commonly prescribed anticonvulsant, used since 1965 as a conventional therapy in partial and generalized tonic-clonic seizures [1, 2]. Unfortunately, in majority of patients the therapy outcome is difficult to predict, due to considerable inter-individual variability in efficacy and safety of the drug [3]. In addition to many other factors, it has been observed that polymorphism of genes involved in drug disposition could influence drug response, leading to development of resistance and/or adverse reactions to epilepsy treatment [1, 4].

Carbamazepine undergoes extensive and complex metabolism that involves several metabolic pathways and multiple enzymes [5–8]. Its ability to induce its own metabolism relies on upregulation of some of the genes engaged in the process, including *CYP1A2* [9–13]. As *CYP1A2* inducibility highly depends on genetic polymorphism [14, 15], its pharmacogenetics could be of importance for carbamazepine pharmacokinetics. Yet, such investigations are currently missing, and the comprehensive knowledge on genetic predictors of the drug's efficacy and safety is still lacking.

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