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ORIGINAL ARTICLE

THE INFLUENCE OF *CYP2C8*3* ON CARBAMAZEPINE SERUM CONCENTRATION IN EPILEPTIC PEDIATRIC PATIENTS

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ABSTRACT

The aim of the present study was to investigate the distribution of *CYP2C8* variants **3* and **5*, as well as their effect on carbamazepine pharmacokinetic properties, in 40 epileptic pediatric patients on carbamazepine treatment. Genotyping was conducted using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and allele-specific (AS)-PCR methods, and steady-state carbamazepine plasma concentrations were determined by high performance liquid chromatography (HPLC). The *CYP2C8 *3* and **5* polymorphisms were found at frequencies of 17.5 and 0.0%, respectively. After dose adjustment, there was a difference in daily dose in *CYP2C8*3* carriers compared to non carriers [mean ± standard deviation (SD): 14.19 ± 5.39 *vs.* 15.46 ± 4.35 mg/kg; $p = 0.5$]. Dose-normalized serum concentration of carbamazepine was higher in *CYP2C8*3* (mean ± SD: 0.54 ± 0.18 *vs.* 0.43 ± 0.11 mg/mL, $p = 0.04$), and the observed correlation between weight-adjusted carbamazepine dose and carbamazepine concentration after dose adjustment was significant only in *CYP2C8*3* non carriers ($r = 0.52$, $p = 0.002$). However, the population pharmacokinetic analysis failed to demonstrate any significant effect of *CYP2C8 *3* polymorphism on carbamazepine clearance [CL L/h = 0.215 + 0.0696*SEX+ 0.000183*DD]. The results indicated that the *CYP2C8*3* polymorphism might not be of clinical importance for epilepsy treatment in pediatric populations.

Keywords: Carbamazepine pharmacokinetics; Children; *CYP2C8*3*; Population pharmacokinetics.

INTRODUCTION

Carbamazepine belongs to the older generation of anticonvulsants, which is almost completely metabolized in the liver through processes that involve several liver enzymes, including CYP2C8 [1-4]. To date, there are 16 different CYP2C8 alleles described http://www.cypalleles. ki.se/cyp2c8.htm), most of them associated with altered enzyme activity [5]. Although genes could affect the drug metabolism there is a general lack of evidence of influence of *CYP2C8* genetic variations on carbamazepine pharmacokinetics, especially in children [6]. Since the drug metabolism in the pediatric population is specific [7], the extrapolation of knowledge from adults, without prior evidence of how various factors influence drug metabolism, may lead to improper management of pediatric therapy [8]. Therefore, the main aim of this study was to investigate the effect of the *CYP2C8* genetic polymorphisms on carbamazepine dosing, serum concentration and clearance, in epileptic pediatric patients.

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