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CYP2C8*3 polymorphism and steady-state carbamazepine plasma concentrations in epileptic patients: preliminary results

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Introduction: Carbamazepine is an important antiepileptic drug that is used for prevention of partial and tonic-clonic seizures. It has a complex biotransformation that involves several drug metabolizing enzymes, including cytochrome P450 2C8 (CYP2C8) [1,2]. Previous studies showed that genetic polymorphism of certain enzymes affects carbamazepine pharmacokinetics [3]. To date, 14 different alleles of the CYP2C8 gene have been described (http://www.cypalleles.ki.se/cyp2c8.htm), and most of them are associated with decreased enzyme activity. The aim of our study was to investigate the possible effect of CYP2C8 genotype on steady-state carbamazepine plasma concentration.

Materials and Methods: Our study involved 40 Serbian epileptic patients (24 male), aged between 5 and 20 years (mean age: 10.7 years) on prescribed carbamazepine treatment. Genotyping for CYP2C8*3 (416G>A, rs11572080), as the most frequent allele responsible for decreased enzyme activity, was performed using PCR-RFLP method. Chi-square test was used to compare obtained with expected allele frequency, i.e. to test the consistency with the Hardy–Weinberg equilibrium. Steady-state carbamazepine plasma concentration was determined by HPLC with UV detection. Observed concentrations were normalized by dose per body weight, and normality of distribution was assessed by Shapiro–Wilk test. Carbamazepine doses and concentrations were correlated using the Spearman analysis. Analysis of variance (ANOVA) was used to assess the effect of CYP2C8*3 on dose-normalized plasma concentrations of carbamazepine.

Results: The allele frequency of CYP2C8*3 was 10%, with 6 (15%) and 1 (2.5%) carriers of CYP2C8*1A/*3 and CYP2C8*1A/*3 genotype, respectively. Both CYP2C8*1A and CYP2C8*3 alleles were in Hardy–Weinberg equilibrium ($\chi 2 = 1.11$; $p=0.05$). Daily carbamazepine doses administered to patients ranged from 220 to 1,600mg (mean±SD: 647.37±252.19mg), i.e. from 7.27 to 35.56mg/kg (mean±SD: 16.13±5.98mg). Mean value of observed carbamazepine plasma concentrations was 6.31±1.72mg/l

(range: 2.89–9.93mg/l). A positive correlation between total daily carbamazepine doses and plasma concentrations was observed (r^2=0.12; r=0.35; p=0.036). On the other hand, daily doses of carbamazepine per body weight did not correlate significantly with observed drug concentrations, but the tendency of positive association was detected (r^2=0.08; r=0.27; p=0.09). Dose-normalized plasma concentrations of carbamazepine (mean±SD) were 0.41±0.14mg/ml, 0.45±0.11mg/ml and 0.50mg/ml in CYP2C8*1A/*1A, CYP2C8*1A/*3 and CYP2C8*3/*3 carriers, respectively. There was a tendency observed in CYP2C8*3 carriers towards higher drug concentrations. However, there was no significant difference in dose-normalized carbamazepine plasma concentrations among CYP2C8 genotype groups (F = 0.32, p=0.73).

Conclusion: The distribution frequency of CYP2C8*3 genetic polymorphism in Serbs correspond well to the data obtained from other Caucasian populations. Carbamazepine plasma concentration in 40 epileptic patients was not significantly affected by CYP2C8*3 polymorphism. Due to small sample size, further investigation is needed to confirm this finding.

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