

Genetic predictors of carbamazepine maintenance dose

Mohd Makmor-Bakry, Nikolas HITIRIS, Elaine BUTLER, Graeme J SILLS, Martin J BRODIE

Epilepsy Unit, Section of Clinical Pharmacology & Stroke Medicine, University Division of Cardiovascular & Medical Sciences, Western Infirmary, Glasgow, Scotland

Background and Objective: Carbamazepine (CBZ) is the second most commonly prescribed antiepileptic drug in the UK. The dose of CBZ required to achieve optimal seizure control varies widely from patient to patient.¹ Multiple hepatic enzymes are involved in the deactivation of CBZ, including CYP3A4, CYP3A5, CYP1A2, UGT2B7 and EPHX1.² Common variation in the genes encoding drug metabolising enzymes (DMEs) may have a significant influence on CBZ concentrations and dosing requirements. We investigated genetic variants in CBZ-related DMEs in an effort to identify predictors of CBZ maintenance dose.

Methods: A total of 400 epilepsy patients from across West of Scotland who provided a DNA sample were included in this study. A subset of patients (n=70; 49% male; median age 34 years, range 14 - 72 years) who were successfully treated with CBZ monotherapy was identified from the study cohort. Patients who did not respond to CBZ or who experienced intolerable side effects were excluded. All 400 subjects were genotyped for common polymorphisms in CYP3A4, CYP3A5, CYP1A2, UGT2B7 and EPHX1 by either conventional polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) or direct sequencing. Genotypes were scored according to the presence of polymorphic alleles. Basic clinical factors and genotype scores were assessed for their ability to predict maintenance doses of CBZ using both univariate and multivariate regression modeling.

Results: There were no significant demographic differences between the CBZ cohort (n=70) and the study cohort (n=400) as a whole and no significant differences in genotype distribution. All genotype frequencies in the CBZ cohort and the study cohort were consistent with Hardy-Weinberg equilibrium ($p>0.05$). Univariate analysis confirmed that no single clinical factor or genetic variant was sufficient to predict CBZ maintenance dose. A multiple logistic regression model incorporating patient age (odds ratio = 1.03, 95%CI 1.00-1.07, $p=0.024$) and genotype of EPHX1 c.337T>C (odds ratio = 0.44, 95%CI 0.22-0.87, $p=0.018$) and EPHX1 c.416A>G (odds ratio = 0.46, 95%CI 0.22-0.98, $p=0.044$) demonstrated a significant association with maintenance dose of CBZ ($r^2=0.16$, $p=0.009$). A dose predictive equation was applied to demonstrate the correlation between observed and expected maintenance dose ($r=0.362$, $p=0.002$).

Conclusion: This analysis suggests that none of the input factors (gender, age, genetic variants) can be used as a single predictor for CBZ maintenance dose. EPHX1 c.337T>C and c.416A>G variants are correlated with CBZ maintenance dose in a predictive model incorporating age. More candidate predictors in a larger population are required to strengthen the model and improve its predictability. A prospective study of CBZ pharmacogenetics in newly diagnosed epilepsy would improve our understanding of the factors influencing individual responsiveness and tolerability.

References

1. Kwan P & Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; 42: 1255-60.
2. Pelkonen O, Myllynen P, Taavitsainen P, *et al*. Carbamazepine: a 'blind' assessment of CYP-associated metabolism and interactions in human liver-derived in vitro systems. *Xenobiotica* 2001; 31: 321-43.