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Genetic predictors of lamotrigine maintenance dose; a role for P-glycoprotein?

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Background and objective: It is increasingly recognised that genetic variability in proteins involved in the pharmacokinetics and pharmacodynamics of therapeutic agents can influence their dosing requirements.[1] Lamotrigine (LTG) is a modern antiepileptic drug. When employed as monotherapy, the dose of LTG required to achieve seizure freedom varies widely from patient to patient. LTG acts on voltage-gated sodium channels and which may be transported across biological membranes by P-glycoprotein (P-gp).[2] Common variation in the genes encoding voltage-gated sodium channel subunits (SCN*) and efflux transporters (ABC*) may have a significant influence on LTG dosing requirements. In this study, we have investigated sodium channel and P-glycoprotein gene variants in an effort to identify predictors of LTG maintenance dose.

Methods: A total of 400 epilepsy patients from across West of Scotland (WSEP) who provided a DNA sample were screened in this study. A subset of 94 epilepsy patients (51% male; median age 38 years, range 17-85 years) who had been seizure-free for at least one year on LTG monotherapy were included in the analysis. Clinical information was extracted from case records. Common genetic variants in *SCN2A* (c.56G>A) and *ABCB1* (c.1236C>T, c.2677G>T/A & c.3435C>T) were identified by polymerase chain reaction - restriction fragment length polymorphism. Genotypes were scored according to the presence of polymorphic alleles: 1 = no polymorphic alleles, 2 = one polymorphic allele, 3 = two polymorphic alleles. Basic clinical factors and genotype scores were assessed for their ability to predict maintenance doses of LTG using both univariate and multivariate linear regression modeling.

Results and discussion: There were no significant demographic differences between the LTG cohort and study cohort (WSEP) as a whole ($p>0.05$). There were no differences in genotype distribution between the LTG and study cohorts and all genotype frequencies were consistent with Hardy-Weinberg equilibrium ($p>0.05$). Univariate analysis revealed that female gender and genotype of the ABCB1 c.1236C>T polymorphism were significantly associated with the maintenance dose of LTG. Univariate analysis suggested that gender ($r^2=0.09$, $p=0.001$) and the *ABCB1* c.1236C>T variant ($r^2=0.06$, $p=0.01$) were associated with LTG maintenance dose. There was no association with age, the *SCN2A* c.56G>A variant or the *ABCB1* c.3435C>T variant. A multivariate model incorporating gender and a multiplicative interaction between c.1236C>T and c.3435C>T variants was sufficiently strong to predict LTG maintenance dose ($r^2=0.17$; $p<0.001$). These genetic polymorphisms of *ABCB1* may have influenced the function of P-gp and consequently altered the absorption and distribution of LTG, which in turn affect the dosage requirement.

Conclusion: This analysis suggests that a combination of gender and genetic variants of the *ABCB1* gene can predict effective maintenance doses of LTG. These findings also lend weight to the potential involvement of P-gp in LTG pharmacokinetics. Further studies incorporating additional clinical factors and genetic variants are required to strengthen the prognostic value of this observation.

References

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