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Pharmacogenetics of uridine diphosphate glucuronosyltransferase (UGT2B7) genetic polymorphism on valproic acid pharmacokinetics in epilepsy

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Background

Sodium valproate is a widely prescribed broad-spectrum antiepileptic drug. It shows high inter-individual variability in pharmacokinetics and pharmacodynamics and has a narrow therapeutic range [1]. We evaluated the effects of polymorphic Uridine diphosphate glucuronosyltransferase (UGT2B7) metabolizing enzyme on the pharmacokinetics of sodium valproate in the patients with epilepsy who showed toxicity to therapy.

Materials and methods

Genotype analysis of the patients was made with polymerase chain–restriction fragment length polymorphism (RFLP) with sequencing. Plasma drug concentrations were measured with reversed phase high-performance liquid chromatography (HPLC) and concentration–time data were analyzed by using a non-compartmental approach.

Results

The results of this study suggested a significant genotypic as well as allelic association with valproic acid toxicity for UGT2B7 polymorphic enzymes. The elimination half-life ($t_{1/2}$=42.2 h) of valproic acid was longer and the clearance rate (CL=947 ml/h) was lower in the poor metabolizers group of UGT2B7 polymorphism who showed toxicity than in the intermediate metabolizers group (t1/2 = 36.5 h, CL = 1,042 ml/h) or the extensive metabolizers group (t1/2 = 27. h, CL = 1,602 ml/h).

Conclusions

Our findings suggest that the UGT2B7 genetic polymorphism plays a significant role in the steady state concentration of valproic acid, and it thereby has an impact on the toxicity of the valproic acid used in the patients with epilepsy.

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