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Pharmacogenetics of Uridine Diphosphate Glucuronosyltransferase (UGT1A9) Genetic Polymorphism on Sodium Valproate Pharmacokinetics in Epilepsy

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Abstract : Background: Sodium valproate is a widely prescribed broad-spectrum anti-epileptic drug. It shows high inter-individual variability in pharmacokinetics and pharmacodynamics and has a narrow therapeutic range. We evaluated the effects of polymorphic uridine diphosphate glucuronosyltransferase (UGT1A9) metabolizing enzyme on the pharmacokinetics of sodium valproate in the patients with epilepsy who showed toxicity to therapy. 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 UGT1A9 polymorphic enzymes. The elimination half-life (t 1/2=40.2 h) of valproic acid was longer and the clearance rate (CL=937 ml/h) was lower in the poor metabolizers group of UGT1A9 polymorphism who showed toxicity than in the intermediate metabolizers group (t1/2=35.5 h, CL=1042 ml/h) or the extensive metabolizers group (t1/2=26. h, CL=1,302 ml/h). Conclusion: Our findings suggest that the UGT1A9 genetic polymorphism plays a significant role in the steady state concentration of sodium valproate, and it thereby has an impact on the toxicity of the sodium valproate used in the patients with epilepsy.

Keywords : UGT1A9, sodium valporate, pharmacogenetics, polymorphism
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