Genetic Polymorphisms of UDP-Glucuronosyltransferases and Plasma Sodium Valproate Level

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Epilepsy is one of the major contributors to pediatric disabilities. Global prevalence of pediatric and adolescence epilepsy is estimated to be 0.5%–1% [1]. In young children sodium valproate is the most commonly prescribed antiseizure drug (ASD) especially in those with idiopathic generalized epilepsy or unclassified generalized epilepsies [2]. It is also the most cost-effective ASD among the ones commonly prescribed. Thus, it is well understood that knowledge regarding the factors affecting its efficacy or drug-related toxicity is of paramount importance.

Valproate is a branched short-chain fatty acid derivative of valeric acid. Three major pathways are involved in the metabolism of valproate. Glucuronidation and beta-oxidation are two predominant pathways responsible for nearly 90% of valproate metabolism in the body. Cytochrome-P dependent oxidation represents a minor route accounting for remaining 10% of the valproate metabolism. Uridine 5'-diphospho-glucuronosyltransferase (UGT) is a family of microsomal glycosyltransferase that participates in glucuronidation reactions. In vitro studies have reported glucuronidation of valproate by *UGT1A3*, *UGT1A4*, *UGT1A6*, *UGT1A8*, *UGT1A9*, *UGT1A10*, and *UGT2B7*. Of these, *UGT1A6* is most commonly studied [3]. Knowledge regarding pharmacokinetics is important to understand difference in response and susceptibility for toxicity of an individual when valproate is used.

Today clinical practice and research is moving towards precision medicine. Unveiling the genetic variations which explain the differences in response to a drug in different individuals with similar disease is an important research topic. The aim is to select a drug that is best suited for an individual rather than for the disease. This is where the importance of the study, published in the current issue, by

Nandith et al. lies [4]. Genetic polymorphism of *UGT* genes affecting function of enzymes can affect serum valproate levels. The current study provides the first published data regarding *UGT2B7* gene polymorphism pattern in Indian pediatric population with epilepsy. *UGT1A6* polymorphism found in the current study was comparable to previous Indian study by Jain et al. [5]. Data regarding association of genetic polymorphism with serum valproate level available from limited studies conducted till date have been inconsistent. This inconsistency in results can be attributed to small sample size. The current study showed no significant association between various genetic polymorphisms of *UGT1A6* and *UGT2B7* and plasma sodium valproate concentration. Almost similar findings were reported by Xu et al. who studied various genetic and nongenetic factors affecting plasma trough concentration-to-dose (C_0/D) ratio of valproic acid in pediatric patients with epilepsy [6]. No significant association was found between common single nucleotide polymorphisms (SNPs) of *UGT2B7* but significant association between the C_0/D ratio and *UGT1A6/9* Del>A was observed in the valproate oral solution group. In fact, this study showed dosage form of valproate to be the most important factor influencing plasma valproate level rather than genetic factors. Thus, the debate remains unresolved whether or not genetic polymorphism of *UGT* genes affect plasma valproate levels.

The current study has laid a foundation for studying genetic polymorphisms of *UGT* gene and its association with serum valproate level in Indian pediatric epilepsy population. Future studies with larger sample size are required to reach a conclusion regarding role of genetic polymorphism of *UGT* genes affecting valproate levels in pediatric epilepsy.

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Declarations

Conflict of Interest None

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