Oral solution and sustained-release tablets of sodium valproate causing significant difference on C_0/D ratio of valproic acid in children with epilepsy

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ABSTRACT

Purpose This study aimed to evaluate potential genetic and non-genetic factors contributing to the variable plasma trough concentration to dose (C_0/D) ratio of valproic acid (VPA) in pediatric patients with epilepsy.

Methods A single-center, retrospective and investigational cohort study was performed by using data from 194 children ages before 1 to 14 years between May 2018 and November 2018. Oral solution (n=135) group and sustained-release (SR) tablets of sodium valproate group (n=59) were defined. VPA C_0 was measured. Twenty-six single-nucleotide polymorphisms (SNPs) were chosen for genotyping by MassARRAY system. Multivariable logistic regression model was used for data analysis.

Results Body weight (BW) and age were positively correlated with C_0/D ratio in a total of 194 patients, but the positive relationship disappeared as they were separated into two subgroups. The average C_0/D value was significantly higher by 2.11-fold (P=0.000) in children who took VPA SR tablets than those were given VPA oral solution. No significant association between genetic variants and variable C_0/D was found, even for the five well-studied SNPs including *UGT2B7* G211T, C802T, C161T, T125C, and *CYP2C9*3* A1075C.

Conclusion It was dosage forms of sodium valproate, not BW, age, or genetic polymorphisms, which significantly impacted the VPA C_0/D ratios in pediatric patients with epilepsy who took oral solution or SR tablets. Our findings indicated that dosage form switching between solution and SR tablets should be performed cautiously. If so, dose tailoring is a feasible strategy, whilst C_0 of VPA, seizure-control effects and adverse reactions are recommended to be closely monitored.

KEYWORDS: Epilepsy; children; valproic acid; C_0/D ratio; dosage form; switching; therapeutic drug monitoring; polymorphism.

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