In response to Gielgens and Bok's commentary on:

Clinical significance of CYP2C9-status guided valproic acid therapy in children

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Our study presented the benefit of CYP2C9-status guided valproate therapy over symptom-driven therapy in children by more precise dosing and by minimizing the risk of side effects, such as increased alkaline phosphatase and hyperammonemia. *CYP2C9* genotyping for loss-of-function mutations can identify patients with permanent poor valproate metabolism; however, inferring the rate of valproate metabolism merely from *CYP2C9* genotype can lead to false prediction. Due to phenoconversion, patients carrying wild *CYP2C9*1/*1* genotype can be switched into transient poor metabolism which can influence the manifestation of valproate side effects.[1] Downregulation of CYP2C9 expression was observed in epileptic patients due to the seizure-induced cytokine release which represses nuclear receptors involved in CYP2C9 expression.[2] Therefore, the ratio of poor CYP2C9 metabolizers is higher than it is predicted from *CYP2C9* genotype. The ratio of low CYP2C9 expresser children in the control and CYPtest groups was still assumed to be similar, since the patients enrolled in this study were all newly diagnosed with epilepsy and were on valproate monotherapy. Thus, misdosing was considered to contribute to the higher ratio of control patients out of the valproate therapeutic range. Toth et al (2015)[2] have reported that the pediatric patients with various CYP2C9-status required different valproate dosing for therapeutic serum concentrations: target valproate dose of 30-40 mg/kg for normal CYP2C9 expressers with *CYP2C9*1/*1* genotype, whereas reduced dose for low expressers and patients carrying loss-of-function mutations. In CYPtest group, we applied the dose of 36.1±6.8 mg/kg for normal expressers carrying *CYP2C9*1/*1*, 17.5±5.7 mg/kg for low expressers and for children with loss-of-function mutations, whereas the dose of 25.0±15.8 mg/kg was applied for control patients.

CYP2C9-status controlled valproate therapy was demonstrated to reduce hyperammonemia in CYPtest children (1/51 in CYPtest group vs 8/47 in control group). The prevalence of hyperammonemia in the control group (17%) was similar to those (15.5%)

reported in pediatric patients under valproate monotherapy by Yamamoto (2013)[3]. The elevation of serum ammonia levels always accompanied with increased alkaline phosphatase and with valproate concentrations higher than 100 μg/ml. Moreover, the children with hyperammonemia both in the control and in CYPtest groups displayed one or some of the secondary symptomes, such as somnolence, fatigue, consciousness or behavior disturbances. Valproate-induced hyperammonemia, which is associated with impaired urea cycle, can occur with normal serum aminotransferase and bilirubin levels. Yamamoto (2012)[4] and Tseng (2014)[5] reported significant correlation between blood ammonia levels and valproate dosage; thus, they suggested to assay ammonia levels, primarily in patients with secondary symptoms.

Although fatal outcome as a consequence of valproate therapy is relatively rare, it is more frequent in pediatric patients, especially in children younger than 2 years of age (1/500), than in adults. On the other hand, the prevalence of hyperammonemia is considered to be high under valproate therapy comparing to non-valproate antiepileptic therapy.[3] We think that the early knowledge of patients' CYP2C9-status and the CYP2C9-status guided treatment can significantly prevent valproate misdosing and the risk of hyperammonemia in children; thus, it can improve the safety of antiepileptic therapy.

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Conflict of interest & Financial disclosure

The authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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