Case Report

Adverse events in a newborn on valproate therapy due to loss-of-function mutations in CYP2C9

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ABSTRACT

An increased risk of valproate-induced toxicity has been reported in children, particularly in those younger than 2 years of age. Significant variations in valproate pharmacokinetics and shifts in the metabolic pathways towards CYP2C9-dependent metabolism seem to play some role in the age-related differences in the incidence of adverse events. We present the case of a premature patient with moderate hemorrhage in the subependymal region (grade II — intraventricular hemorrhage without ventricular dilatation), several myoclonic episodes in her right upper arm (series of jerks lasting milliseconds), and epileptiform abnormalities on the EEG (localized spike-and-wave in the left frontal region with preserved background activity) who was treated with valproate. Serious side effects, consisting of bone marrow depression, hyperammonemia, and serum alkaline phosphatase elevation, were observed seventeen days after the beginning of valproate therapy. The toxic symptoms were likely the consequence of a reduced ability to metabolize valproate. The patient was demonstrated to carry two loss-of-function mutations in CYP2C9 (CYP2C9*3/*3) resulting in exaggerated blood concentrations of valproate. The present case highlights the importance of assaying inborn errors in valproate. The patient was treated with phenobarbital (2 mg/kg) on the 7th day of age. Because there is a high risk of serious cognitive effects impacting attention and memory in children from chronic and long-term phenobarbital treatment, we replaced phenobarbital with valproate with the target dose of 30 mg/kg for the premature patient. Seventeen days after the beginning of valproate therapy, the patient displayed signs of bone marrow depression (hematocrit: 17.7%, hemoglobin: 59 g/l, white blood cell count: 5.1 × 10⁹/l, platelet count: 39 × 10⁹/l), hyperammonemia (92 μmol/l), and serum alkaline phosphatase elevation (1695 units/l). The toxic symptoms were attributed to the valproate treatment; therefore, it was promptly and completely terminated. Ten days after withdrawal, the serum level of valproate was still as high as 19.5 μg/ml, which was...
determined by liquid chromatography–tandem mass spectrometry. The hemoglobin level was ameliorated by transfusion of a leucodepleted red-blood-cell concentrate, whereas platelet count and white blood cell count were spontaneously normalized within 6 days. The blood ammonia level and serum alkaline phosphatase were gradually recovered after 10 days and 1 month, respectively.

3. Discussion

Glucuronidation is poorly developed in neonates and young children, whereas mitochondrial β-oxidation activity has been reported to be compromised by valproate and some of its metabolites. As a consequence, CYP-catalyzed oxidation, with the major contribution from CYP2C9, becomes the principal route of metabolism in pediatric patients [2]. It inspired us to identify the loss-of-function mutations in CYP2C9 genes in this premature patient. CYP2C9 genotyping for the polymorphic CYP2C9*2 and CYP2C9*3 alleles was performed retrospectively in the patient’s peripheral blood sample, according to the methods of Temesvári et al. [3]. The assay revealed the homozygous mutant CYP2C9*3/*3 genotype which can account for the substantially reduced ability of the child to metabolize valproate. Although the serum concentration of valproate was assayed after the termination of valproate treatment, on the basis of the high level measured ten days after withdrawal, we assumed extremely high exposure during the valproate therapy which we attributed to the poor metabolism of valproate as a consequence of the homozygous mutant CYP2C9 genotype. The exaggerated blood concentration was likely the cause of toxic symptoms in the premature girl.

Valproate is routinely initiated at low dosages (10–15 mg/kg), and the target doses are subsequently titrated until the optimal clinical response is achieved. Valproate blood concentrations are generally assayed three to four weeks after the beginning of therapy; thus, symptoms, adverse reactions, and ineffectiveness can inform clinicians about valproate misdosing in the early period of therapy. Compared to dosing based on symptoms, the dosing based on the status of CYP2C9 has been reported to reduce the incidence of exaggerated valproate blood concentrations, increased serum alkaline phosphatase activity, and valproate-evoked serious side effects, notably hyperammonemia, in children [4]. Therefore, allelic variants in the CYP2C9 gene should be assayed before the beginning of antiepileptic therapy in pediatric patients.

Because the prevalence of patients with two polymorphic CYP2C9 alleles (CYP2C9*2/*2, CYP2C9*3/*3 or CYP2C9*2/*3) is relatively high in European white populations (approximately 2–10%), clinicians should be vigilant for pediatric patients with two loss-of-function CYP2C9 alleles. To avoid serious adverse reactions as a consequence of inborn errors in valproate metabolism, nonvalproate antiepileptic therapy can be proposed for children with two mutated CYP2C9 alleles.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

References

[1] Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. Epilepsia 2002;43(Suppl. 3):53–9.
[2] Tóth K, Bődi T, Kiss Á, Temesvári M, Háfra E, Nagy A, et al. Phenocconversion of CYP2C9 in epilepsy limits the predictive value of CYP2C9 genotype in optimizing valproate therapy. Pers Med 2015;12:201–9.
[3] Temesvári M, Kóbori L, Paulik J, Sárváry E, Belic A, Monostory K. Estimation of drug-metabolizing capacity by cytochrome P450 genotyping and expression. J Pharmacol Exp Ther 2012;341:294–305.
[4] Bődi T, Tóth K, Nagy A, Szever Z, Kiss Á, Temesvári M, et al. Clinical significance of CYP2C9-status guided valproic acid therapy in children. Epilepsia 2015;56:849–55.