Severe phenytoin toxicity in a CYP2C9*3*3 homozygous mutant from India

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Case Report

A 22-year-old lady (weight, 38kg; height, 145cm) had been on long-term DPH therapy (12 months) for primary generalized epilepsy at a variable daily dose of 200-300-mg/day. Though she was advised sodium valproate initially, this had to be replaced by DPH since the patient could not afford the former while the latter was freely supplied in the hospital. In July 2002, she was hospitalized with adverse effects and poor compliance of DPH with resultant poor control of seizures. On neurological examination, this patient was found to have nystagmus, ataxia and excessive sedation. Physical examination also revealed lymphadenopathy, pain and deformity of multiple bones, anemia, hirsutism, acne and gum hypertrophy (Grade III). Skeletal survey revealed multiple fractures at various stages of healing along with features suggestive of osteomalacia. Hemoglobin level, plasma albumin level and body mass index (BMI) were 6.5 gm %, 3.3 g/dl and 18.1 respectively. Phenytoin (DPH) toxicity was suspected and plasma DPH was estimated in the patient by reverse phase HPLC method as described by Gerson et al. The DPH level was 33.2 mg/L at prescribed dosage of 300 mg/day of DPH over the preceding one month period. The DPH was stopped and the acute toxicity symptoms subsided immediately. The DPH was substituted with sodium valproate whose compliance was monitored and ensured without any adverse effects. Over a period of six months, seizures remained well controlled. Clinically, gum hyperplasia (Grade I), acne, hirsutism and anemia had also

Key words: CYP2C9 polymorphism, phenytoin toxicity

Phenytoin / Diphenyl hydantoin (DPH) is a well-established, widely prescribed first line drug for the treatment of simple and complex partial seizures as well as generalized seizures. It is metabolized by cytochrome P450 enzyme CYP2C9 (90%) and CYP2C19 (10%). The rate of metabolism of DPH is genetically determined and varies by ethnicity and race. In the Tamil Nadu population, the frequency of CYP2C9 alleles viz. CYP2C9*1, CYP2C9*2, CYP2C9*3 has been established. The distribution of CYP2C9*2 and *3 mutant alleles in our population (0.04 and 0.08) was less than that of the Caucasians (0.12 and 0.08) but more than that of Orientals (0.00 and 0.03).[1]

The authors report an Indian adult female patient with a history of generalized tonic clonic seizures who developed severe features of phenytoin (DPH) toxicity on therapeutic dosage of this antiepileptic drug. Administration of 300mg/day of DPH in this patient resulted in toxic symptoms associated with an excessive serum DPH concentration of 33μg/ml. The PCR-RFLP analysis revealed a homozygosity involving CYP2C9*3*3. This mutation results in a marked decrease in the enzymatic activity (CYP2C9) and leads to a decreased clearance of the drug which can lead to severe acute and chronic toxicity. On switching the antiepileptic therapy from DPH to sodium valproate, there was reversal of both.

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reversed significantly.

The clinical and plasma level evidences of DPH toxicity prompted appropriate pharmacogenomics studies. Patient’s DNA was extracted from peripheral blood leucocytes by conventional phenol-chloroform method and genotyping of CYP2C9 for *1, *2 and *3 alleles was performed by a polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) method. The CYP2C9*2 (Arg144Cys) was detected using the forward and reverse primers 5’ TACAAATACAATGAAAATATCATG 3’ and 5’ CTAACAACCAGA TCATATACT 3’, respectively. The amplified PCR products were digested with 5 U restriction enzymes AvalI by overnight incubation at 37°C.

The detection for CYP2C9*3 (Ile359Leu) was performed using two separate mismatched forward PCR primers 5’ AATAATAATATGCAGGTCCAGAGATGC 3’ and 5’ AATAATAATATGCAGGTCCAGAGGTAC 3’ and an intron 7 reverse primer 5’ GATACTATGAATTTGGGACTT C3’. The first mismatched primer introduced an NsiI site in Ile359 and the second mismatched forward primer introduced a KpnI site in Leu359 alleles. The amplified PCR products were digested with 5 U restriction enzymes NsiI and KpnI by overnight incubation at 37°C.

The digested PCR products were separated by electrophoresis using an 8% polyacrylamide gel and stained with ethidium bromide. Samples containing PCR-RFLP method. The CYP2C9*3*3 was identified the unfavorable genotype of CYP2C9, a major DPH metabolizing enzyme in this case, and prompted the physicians to choose and convince the patient on the need for an alternate antiepileptic drug such as sodium valproate. This would have avoided a number of iatrogenic complications of antiepileptic drug therapy in this case, which resulted in poor drug compliance and poor seizure control as well. The fact that the same enzyme also metabolizes drugs like warfarin, tolbutamide, losartan, diclofenac etc adds to the value of this genotyping since many elderly epileptic patients have co-morbidity and could be candidates for co-prescription with these drugs as well. We recommend that wherever possible, the clinicians may do CYP2C9 genotyping of the epileptic patients before prescribing DPH.

**Discussion**

A 22-year-old lady with epilepsy on chronic DPH therapy had definite features of acute DPH toxicity at hospitalization which was documented by plasma DPH concentration with central nervous system intoxication. Ther Drug Monit 2000;22:239-2.

After switching from DPH to sodium valproate, seizures remained well controlled and her acute toxicity symptoms disappeared. On follow-up for six months, there was a significant reduction in the chronic toxicity features as well. It was obvious that DPH was not to be the drug of choice for primary generalized epilepsy in this patient. Pharmacogenomics studies before initiating antiepileptic therapy could have easily identified the unfavourable genotype of CYP2C9, a major DPH metabolizing enzyme in this case, and prompted the physicians to choose and convince the patient on the need for an alternate antiepileptic drug such as sodium valproate. This would have avoided a number of iatrogenic complications of antiepileptic drug therapy in this case, which resulted in poor drug compliance and poor seizure control as well. The fact that the same enzyme also metabolizes drugs like warfarin, tolbutamide, losartan, diclofenac etc adds to the value of this genotyping since many elderly epileptic patients have co-morbidity and could be candidates for co-prescription with these drugs as well. We recommend that wherever possible, the clinicians may do CYP2C9 genotyping of the epileptic patients before prescribing DPH.

**References**


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