Phenytoin Toxicity in a Korean Patient Homozygous for CYP2C9*3

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Abstract

We report a case of phenytoin toxicity due to impaired drug metabolism in a patient homozygous for CYP2C9*3. A 46-year-old woman was taking phenytoin to prevent postoperative seizures. She attained high serum phenytoin levels at the standard doses (300 mg/day) and developed symptoms of phenytoin toxicity including blurred vision, nausea and headache. The patient was treated with reduced doses of phenytoin and then phenytoin therapy was finally discontinued. Genotyping for CYP2C9 revealed that this patient had a homozygous genotype, CYP2C9*3 /*3. This is the first Korean case of phenytoin toxicity with homozygous CYP2C9*3. This case suggests the clinical usefulness of pharmacogenetic testing for individualized dosage adjustments of phenytoin.

Phenytoin is a widely prescribed anticonvulsant. Due to the significant interindividual variability and non-linearity in its pharmacokinetics, estimation of the optimal phenytoin dose for each patient is difficult. Common adverse effects associated with phenytoin therapy include nystagmus, blurred vision, ataxia, dysarthria, drowsiness and coma[1,2]. These dose-related toxicities usually occur in association with toxic serum concentrations of phenytoin.

The major pathway for phenytoin elimination is via 4'-hydroxylation to form 5-(4 p-hydroxylphenyl)-5-phnylhydantoin[1-5]. Phenytoin is metabolized predominantly by CYP2C9, which accounts for 80-90% of all metabolic products, with a minor contribution by CYP2C19[6,7].

Genetic polymorphisms of the CYP2C9 are responsible for the inter-individual variability found in phenytoin pharmacokinetics[5,8,9]. Many studies have clearly demonstrated a significantly reduced activity in carriers of the CYP2C9 allelic variants such as CYP2C9*2 and CYP2C9*3[4,5,10,11]. Homozygous carriers of CYP2C9*3 may have substantially reduced activity, with CYP2C9-mediated clearance of about 4-6% compared with homozygous carriers of the wild type allele[12].

In this report, we present the first Korean case of phenytoin intoxication in a patient with the genotype CYP2C9*3/*3, which resulted in markedly decreased activity of CYP2C9. This resulted in high serum phenytoin concentrations that were associated with adverse effects after standard doses of phenytoin administration in the patient presented here.

The patient was started on phenytoin therapy to prevent postoperative seizures. Three days after starting phenytoin therapy (300 mg/day), the serum phenytoin level was found to be 23.62 mg/L. The patient reported blurred vision and headache. The phenytoin dosage was reduced to 200 mg/day. Two months later, the serum phenytoin concentration was 18.62 mg/L, still high but in the recommended therapeutic range (10-20 mg/L). The physician discontinued the phenytoin therapy and requested pharmacokinetic consultation. The volume of distribution (Vd), Michaelis-Menten constant (K_m) and maximal elimination rate (V_{max}) were 0.65 L/kg, 9.73 mg/L and 3.06 mg/kg/day, respectively. The patient was found to be a poor metabolizer with the genotype CYP2C9*3/*3 (Fig. 1) and CYP2C19*1/*1. The patient completely recovered from the symptoms of the phenytoin intoxication after the phenytoin withdrawal.

Discussion

Genetic polymorphisms of CYP2C9 cause significant variability among individuals with regard to drug response[5,8,9,13]. Patients with genetic variants of CYP2C9 have higher serum phenytoin levels and a higher risk for phenytoin intoxication.

More than 20 variant alleles of CYP2C9 had been reported (URL: http://www.imm.ki.se/CYPalleles/cyp2c9.htm). Many previous studies have demonstrated that two common variants CYP2C9*2 and
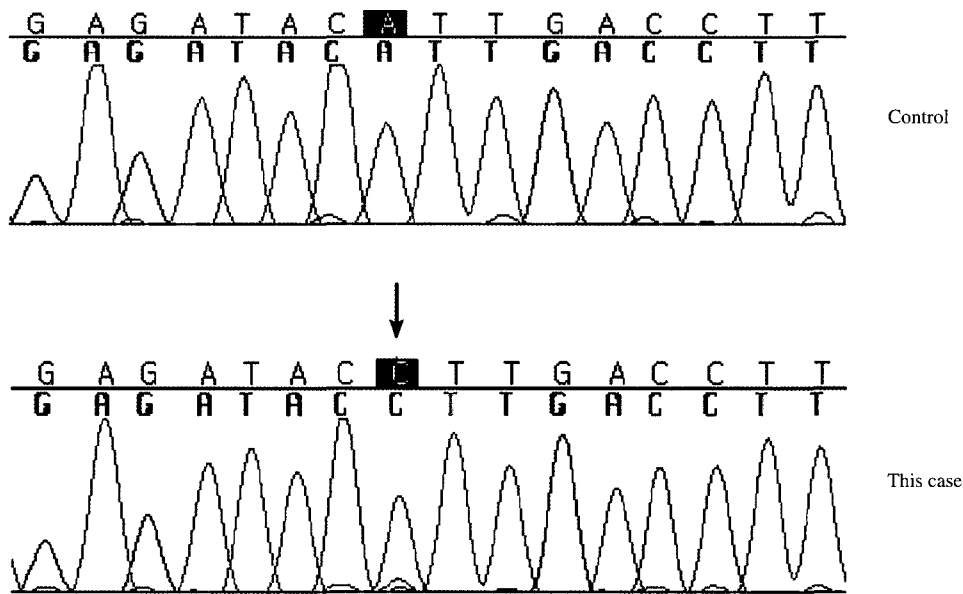
Fig. 1. Detection of nucleotide change by sequencing analysis of *CYP2C9* gene in this patient with *CYP2C9*3/*3* showing homozygous A1075C (Ile359Leu) substitution (indicated by an arrow).

*CYP2C9*3* are associated with reduced catalytic activity of CYP2C9[4, 8,10,11,14]. Therefore, subjects who are homozygous or heterozygous for these variant alleles should be treated with reduced maintenance doses of CYP2C9 substrates such as phenytoin and warfarin. Allele frequencies of *CYP2C9* variants have been shown to be markedly different in different populations. Caucasians have higher frequencies of *CYP2C9*3* than Asians (6-10% vs 2-5%)[5,8,9]. There have been no documented Asian carriers of the *CYP2C9*2* variant, while 8-20% of Caucasians appear to have the *CYP2C9*2* allele (1-11). Yoon *et al.*[15] reported that from a pool of 574 Koreans 2.3% were heterozygous for *CYP2C9*3* and none were found to be carriers of *CYP2C9*2*.

There have been some case reports on severe phenytoin intoxication in subjects with genetic variants of the *CYP2C* subfamily. A severe phenytoin intoxication in a subject homozygous for *CYP2C9*3* has been previously reported[16,17]. In a Japanese report, an adult male patient with *CYP2C9*1/*3* and *CYP2C19*1/*3* had toxic symptoms and excessive serum phenytoin concentrations[18].

This is the first report of a Korean patient with the *CYP2C9*3/*3* genotype showing phenytoin intoxication. Our patient had a high serum phenytoin level at standard doses and experienced adverse drug effects. There are many conditions other than genetic polymorphisms that could alter the phenytoin metabolism. However, in this patient, we could not identify

any specific pharmacokinetic or pharmacodynamic factors associated with the phenytoin intolerance, such as drug interactions or underlying disease. Therefore, a pharmacogenetic test was performed to explore the possible genetic factors contributing to the unusual drug response. This patient could have taken the appropriate therapeutic measures earlier, and be maintained on a safer regimen with lower doses, if she had been genotyped at the beginning of phenytoin therapy.

There is a strong association between *CYP2C9* allelic variants and phenytoin dose requirement. About 30% of the interindividual variability in phenytoin trough levels is explained by *CYP2C9* genotypes[19]. According to Van der Weide *et al.*[11], for patients carrying at least one mutant *CYP2C9* allele, the mean phenytoin dose required to achieve a therapeutic serum concentration was about 37% lower than the mean dose required by wild-type individuals (199 mg/day vs. 314 mg/day).

Our patien's K_m and V_{max} were 9.73 mg/L and 3.06 mg/kg/day. These are 2.5-fold higher and 2.0-fold lower, respectively, than the values reported by Mamiya *et al.*[4], who reported that the population mean K_m and V_{max} were estimated to be 4.0 mg/L and 6.07 mg/kg/day, respectively in a Japanese patient population with the normal *CYP2C9* and *CYP2C19* alleles. The V_{max} of phenytoin among patients with heterozygous *CYP2C9*3* was 33% lower than that among patient with the wild type *CYP2C9*, in a Japanese

study by Odani et al.[14]. CYP2C19 is also involved in the phenytoin metabolism, although its relative contribution to phenytoin pharmacokinetics is smaller than CYP2C9. The V_{max} values of phenytoin was slightly decreased (up to 14%) among Japanese patients with CYP2C19 mutations compared to patients with normal CYP2C19[14].

We demonstrated that the metabolism of phenytoin was markedly impaired in a patient with homozygous CYP2C9*3; the CYP2C9 variant is associated with a risk of phenytoin intoxication. At present, genotyping is not currently routinely performed in clinical practice; clinicians adjust the phenytoin dose based on serum phenytoin measurement and clinical response. However, additional CYP2C9 genotyping may serve as an important guide for safer dosage adjustment and prediction of drug response in each individual patient on phenytoin therapy. CYP2C9 genotyping may help in reduce adverse effects and increase efficacy of phenytoin treatment. Characterization of CYP2C9 polymorphic alleles may identify patients at risk, so that phenytoin can be prescribed more cautiously in patients with decreased enzyme activity of CYP2C9.

Methods

A 46-year-old woman presented to the emergency room complaining of sudden onset of headache and nausea. Brain CT and angiography revealed subarachnoid hemorrhage with a middle cerebral artery aneurysm. Surgery was performed for the aneurysm.

The patient was started on phenytoin therapy to prevent postoperative seizures; just after the surgery a single IV loading dose of phenytoin of 300 mg was followed by an oral maintenance dose of 100 mg three times a day (300 mg/day). Her body weight was 65 kg and she was 170 cm in height. Her prescription medication also included dexamethasone, ranitidine, mannitol, nimodipine, astromicin, ceftriaxone, levosulpride, acetaminophen, and sucralfate. One day after starting phenytoin therapy, serum phenytoin measurement by fluorescence polarization immunoassay (TDxFlx, Abbott, USA) showed a concentration of 11.15 mg/L. Three days later, the serum phenytoin level was found to be 23.62 mg/L. The patient reported blurred vision and headache. Her vital signs were stable and results of routine laboratory tests were within normal limits. The liver and renal function test profile was unremarkable and the serum albumin level was 4.4 mg/dL. The patient was discharged after a total of nine days of hospitalization without any dose adjustment for the phenytoin therapy. After two weeks the patient visited the outpatient clinic complaining of blurred vision, nausea and headache. The phenytoin dosage was reduced to 200 mg/day. Two months later, the serum phenytoin concentration was 18.62 mg/L.

The pharmacokinetic parameters for this patient were estimated by Baysian analysis using the Abbott-base Pharmacokinetic system (Abbott, USA). The patient was genotyped for CYP2C9 and CYP2C19 by PCR and sequencing (all 9 exons for CYP2C9, exon 4 and 5 for CYP2C19) after written informed consent. DNA was extracted from peripheral blood leukocytes. The PCR products were sequenced using the ABI PRISIM BigDye terminator Cycle Sequencing Kit and an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, USA). Primers used and PCR conditions in this study are available upon request.

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