

NEUROLOGY

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Neurology 2003;60;1395-1396

This information is current as of November 24, 2009

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G. Citerio, MD; A. Nobili, MD; L. Airoidi, PhD; R. Pastorelli, PhD; and A. Patrino, MD

Phenytoin is metabolized by cytochrome P450 enzyme CYP2C9. The rate of metabolism is genetically determined and varies by race.^{1,5} In white populations there are three CYP2C9 alleles: CYP2C9*1, CYP2C9*2, and CYP2C9*3, with frequencies of 77%, 14%, and 9%.^{2,3} The mutant alleles CYP2C9*2 and CYP2C9*3 differ from the wild-type CYP2C9*1 by a single point mutation and are associated with 30% (allele 2) and 85% (allele 3) lower enzymatic activity.^{2,3} Thus, in individuals carrying at least one mutant CYP2C9 allele, the mean phenytoin dose required to achieve therapeutic serum concentrations is 30 to 40% lower than in those with the wild-type allele.^{1,3} Since phenytoin has a narrow therapeutic index, a toxic serum concentration (>20 mg/L) can be reached.⁴

Case report. A 41-year-old woman was admitted to the emergency department after a seizure. She was alert but mute, responsive to orders, and had a right hemiparesis. Soon after admission, seizures recurred and were treated with diazepam (10 mg repeated twice, infused in 10 minutes), with cessation of seizures. Brain CT showed a left frontal lobe tumor. The patient was transferred to the neurosurgical department, and 1 hour later seizures started again. Phenytoin (15 mg/kg in 30 minutes) was infused. Two hours later, the patient had a low respiratory rate (5 breaths/minute) and blood pressure of 110/50 mm Hg. She was no longer able to respond to orders, utter words, or open her eyes. After a

painful stimulus, the best motor response was a left-sided movement and right flexion (Glasgow Coma Score M5, V1, E1).

The patient was promptly intubated and the plasma phenytoin level was tested. Subsequently she developed hypotension (systolic blood pressure 80 mm Hg) and was transferred to the intensive care unit where, in spite of infusion of crystalloid and colloid and increasing doses of dopamine and noradrenaline, the hypotension did not improve (systolic blood pressure 70 mm Hg with relative bradycardia 68 beats per minute). Transthoracic echocardiography showed no cardiac lesion. The initial phenytoin plasma level was 79 µg/mL, and the phenytoin plasma concentration was monitored daily for 8 days. On day 3 after hospital admission, multiple oral doses of activated charcoal were administered⁶ and plasma phenytoin dropped steadily (figure).

Her condition improved. On day 6 the patient was extubated and topiramate 25 mg twice daily was started. On day 7 she was transferred to the neurosurgical department, where the brain tumor was removed. Histologic examination indicated it was an oligodendroglioma. One week after surgery, the patient was discharged without deficits.

A review of the case suggested impaired phenytoin metabolism. The patient was therefore screened for genetic polymorphism of CYP2C9. Genotyping for the CYP2C9*2 and CYP2C9*3 alleles was done on peripheral blood DNA by PCR-restriction fragment length polymorphism analysis.^{1,2,7} She was heterozygous for the CYP2C9*3 allele. The CYP2C9*1/CYP2C9*3 genotype was confirmed by automated sequencer analysis. This genotype may be responsible for the toxic phenytoin levels. Furthermore, the patient's brother had been operated on 3 years earlier for a low-grade glioma and in the postoperative period had presented a biliary ductular vanishing syndrome after prophylactic infusion of phenytoin. Thus, other family members were screened for CYP2C9 polymorphism, but only the brother who had shown hepatic toxicity after phenytoin was positive for the mutation (CYP2C9*1/CYP2C9*3 genotype).

Discussion. This case illustrates the potential value of genotyping tests for impaired metabolism of drugs with a narrow therapeutic index. The genotyping of other family members may be indicated to avoid adverse events related to other commonly used drugs, such as NSAIDs, fluoxetine, or warfarin, which are metabolized by CYP2C9.

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Received August 14, 2002. Accepted in final form January 9, 2002.

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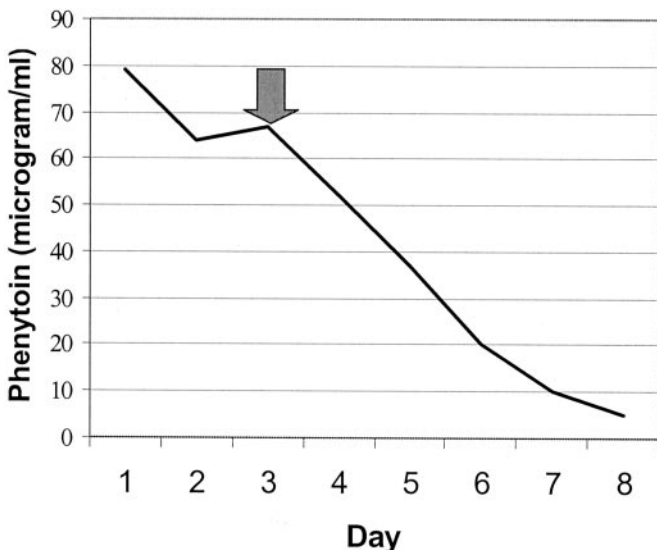


Figure. Daily monitoring of the drug plasma concentration after a single phenytoin bolus showed the progressive decrease in plasma levels. On day 3 (arrow), multiple oral doses of activated charcoal were administered, and plasma phenytoin dropped steadily.

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Correction

In the article “Practice Parameter: Temporal lobe and localized neocortical resections for epilepsy: Report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons” (*Neurology* 2003;60:538–547), table 1 on p.540 was incorrect. The correct table is:

Table 1 AAN evidence classification scheme for a therapeutic article

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.

The following are required:

- a) Primary outcome(s) is/are clearly defined.
- b) Exclusion/inclusion criteria are clearly defined.
- c) Adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias.
- d) Relevant baseline characteristics are presented and substantially equivalent among treatments groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomized, controlled trial in a representative population that lacks one criteria a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

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