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Extreme Warfarin Sensitivity in Siblings Associated With Multiple Cytochrome P450 Polymorphisms

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Warfarin use is complicated by an erratic dose response. Warfarin is metabolized by two distinct subfamilies of the cytochrome P450 (CYP) complex. We describe two siblings with extreme sensitivity to warfarin who share an unusual CYP genotype. These individuals illustrate both the importance of genetics in influencing the metabolism of warfarin as well as the potential utility of genetic testing as a guide to prescribing this medication. Am. J. Hematol. 67:144–146, 2001.

Key words: warfarin; cytochrome P450 complex; siblings

INTRODUCTION

Warfarin is one of the most frequently prescribed medications in the United States [1]. Warfarin use, however, is complicated by a narrow toxic–therapeutic index coupled with an unpredictable dose response [2]. It is becoming increasingly appreciated that an individual's sensitivity to warfarin may be largely genetically determined. We describe two siblings with extreme sensitivity to warfarin who share an unusual genotype of the cytochrome P450 complex (CYP). These individuals illustrate both the importance of genetics in influencing the metabolism of this commonly used medication and the potential utility of genetic testing as a guide to warfarin prescription.

CASE REPORT

An 81-year-old Caucasian female was prescribed warfarin, 5 mg daily, for chronic atrial fibrillation. This was subsequently discontinued after 1 week due to an episode of severe epistaxis. She presented to her physician's office 3 weeks following her last warfarin dose for routine follow-up. Her physical examination was unremarkable. However, she was found to have an International Normalized Ratio (INR) exceeding 8.0 (normal 0.8–1.2), a prothrombin time of 32.5 sec (11.0–13.0 sec), and a plasma warfarin concentration of 1.3 μg/ml. An activated partial thromboplastin time (aPTT) of 39.5 sec (normal 21.1–32.1 sec) normalized following incubation with control plasma, consistent with clotting factor deficiency. Her hepatic function profile, serum albumin, and other laboratory studies were within normal limits. The patient was admitted to the hospital, placed on bed rest, and treated with fresh frozen plasma and vitamin K. Her coagulopathy resolved, and she was discharged after an uneventful course. Of note, her brother was also extremely sensitive to warfarin, receiving 0.75 mg daily for atrial fibrillation.

As part of an Institutional Review Board-approved protocol, both siblings underwent CYP genotyping. Briefly, genomic DNA was isolated from peripheral blood leukocytes, amplified by polymerase chain reaction using standard techniques, and screened for variants of CYP2C9 and CYP2A6 subfamilies associated with altered warfarin metabolism as previously described [3,4]. The siblings were determined to be homozygous for the CYP2C9*3 allele and heterozygous for the CYP2A6*1/2 allele (Fig. 1A,C). These findings were confirmed by fluorescent dye-terminator automated DNA sequencing (Fig. 1B,D).

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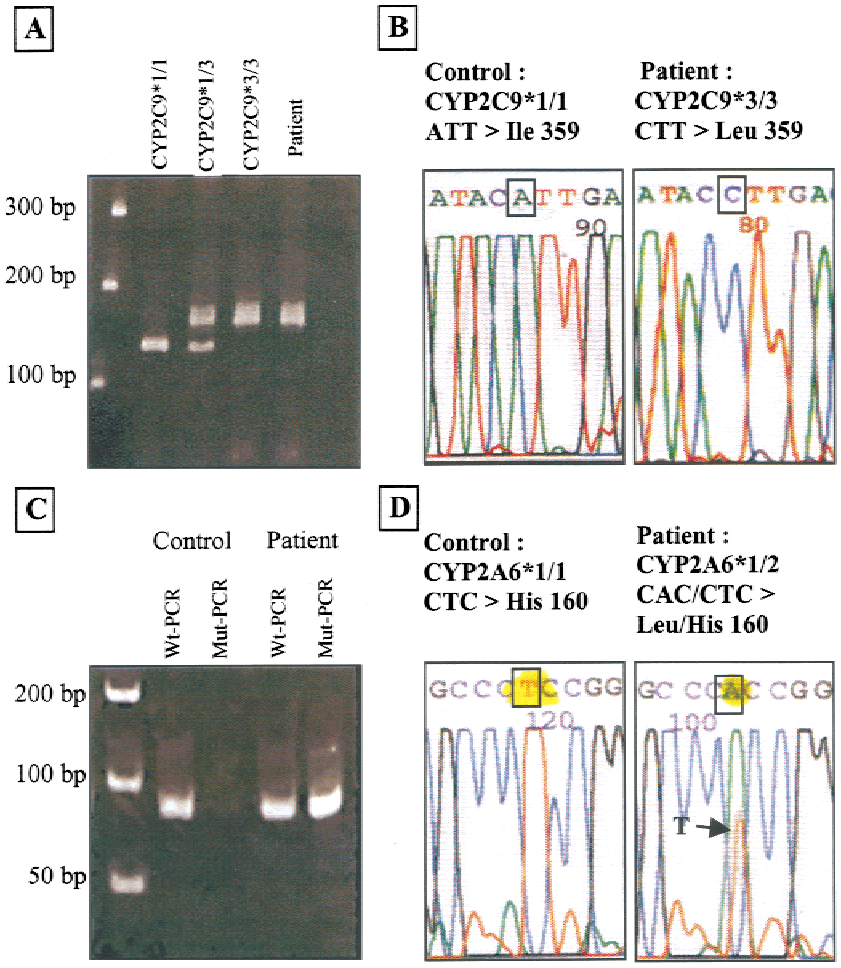

Fig. 1. (A) PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) assay for CYP2C9*1/3. Lane 1: 50–2,500-base pair (bp) size marker. Lane 2: wild-type control (CYP2C9*1/1) (112-bp fragment). Lane 3: heterozygote control (CYP2C9*1/3) (112-bp and 141-bp fragments). Lane 4: homozygote control (CYP2C9*3/3) (141-bp fragment). Lane 5: Patient sample. (B) Fluorescent sequencing of a wild-type control and the patient demonstrating the presence of the isoleucine to leucine change at position 359 for the CYP2C9*1/3 allele. The patient genotype is CTT at both CYP2C9 alleles instead of ATT, signifying an amino-acid substitution (Ile > Leu). (C) PCR-RFLP assay for the CYP2A6*1/2 allele. Lane 1: 50–2,500 (bp) size marker. Lanes 2 and 3: wild-type control. Lanes 4 and 5: patient sample. (D) Fluorescent sequencing of a wild-type control and for the CYP2A6*1/2 allele. The patient is heterozygous at codon 160 (CAC/CTC), as indicated by overlapping signals at the second position for both A and T. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

The effective half-life of warfarin is approximately 40 hr [5]. Thus detection of warfarin 3 weeks after it was last administered reflects a marked impairment of warfarin clearance, suggesting that our patient's hypersensitivity to warfarin resulted from reduced metabolism. Warfarin is a racemate, with the *S*-enantiomer possessing the predominant anticoagulant activity [2]. The CYP2C9 subfamily is the principal pathway for *S*-warfarin metabolism, with the CYP2A6 subfamily possibly serving a minor role [6,7]. Recently, point mutations of the 2C9 (designated 2C9*2 and 2C9*3) and 2A6 (designated 2A6*2) subfamilies have been described [8,9]. These point mutations are associated with a decrease in the catalytic efficiency of CYP for *S*-warfarin, in vitro, and with increased sensitivity to warfarin clinically [8–10]. Thus the extreme warfarin sensitivity present in our patient and her sibling appears to be the result of their unusual genotype (e.g., homozygous for CYP2C9*3 and heterozygous for CYP2A*1/2).

Hemorrhagic complications of warfarin are most common in the weeks and months after therapy is started, due in part to the unpredictable dose–response relationship of this medication. As our cases illustrate, genetic variants of CYP may underlie an exaggerated anticoagulant response and place patients at increased risk of significant hemorrhage when warfarin is administered at conventional doses [10]. As the frequency and effects of CYP polymorphisms become more completely understood, genotyping may provide a useful means of both identifying patients at risk for complications as well as predicting warfarin dosing, thereby enhancing the safety of this medication.

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