

A Case of Intolerance to Warfarin Dosing in an Intermediate Metabolizer of CYP2C9

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We report a case of intolerance to warfarin dosing due to impaired drug metabolism in a patient heterozygous for the *CYP2C9**3 allele. A 30-year-old woman with an artificial cardiac pacemaker was taking warfarin to prevent thromboembolism. This patient had an extremely elevated international normalized ratio (INR) of prothrombin time (PT) following standard doses of warfarin and experienced difficulties during the induction of anticoagulation. Genotyping for *CYP2C9* revealed that this patient was an intermediate metabolizer with genotype *CYP2C9**1/*3. This case suggests the clinical usefulness of pharmacogenetic testing for individualized dosage adjustments of warfarin.

Key Words: Warfarin, cytochrome P-450 CYP2C9, polymorphism, prothrombin time, pharmacogenetics

INTRODUCTION

Warfarin, a widely used anticoagulant, may increase the risk of bleeding complications with narrow therapeutic index.¹⁻³ The prolongation of the prothrombin time (PT) remains the primary way to measure the anticoagulant effect of warfarin. Because warfarin is subject to great variability between individuals in its pharmacokinetics with effective daily doses ranging from 0.5 mg to 60 mg,⁴ therapy should be individualized by monitoring patient's international normalized ratio

(INR) of PT.

Warfarin metabolism is catalyzed by CYP2C9, which metabolizes S-warfarin to inactive S-7-hydroxywarfarin.⁵ A genetic polymorphism of *CYP2C9* contributes to variability among patients for required maintenance doses of warfarin. Multiple studies have clearly demonstrated an increased frequency of *CYP2C9* allelic variants such as *CYP2C9**2 and *CYP2C9**3 in patients stabilized on low-dose warfarin therapy and have established relations between genetic deficiency in *CYP2C9* enzyme activity with increased likelihood of extremely elevated INRs and major bleeding events, compared with the general population.⁶⁻¹¹

In this report, we present a case of warfarin therapy in a patient with the variant *CYP2C9**1/*3, which resulted in decreased activity of *CYP2C9*. Extremely prolonged PT during the induction phase of standard warfarin therapy was found and a reduction of warfarin dosage was required to get the target INR in this case.

CASE REPORT

A 30-year-old woman with an artificial cardiac pacemaker presented to the clinic complaining of dizziness and dyspnea. The patient had a history of hypertrophic cardiomyopathy with complete atrioventricular block and the pacemaker had been implanted in her 13 years before presentation. Her prescription medication for the previous 2 years included lasix 20 mg, spironolactone 12.5 mg, imidapril 2.5 mg, and teprenone 50 mg twice a day.

She had suffered from dizziness and dyspnea

Received July 12, 2004
Accepted August 23, 2004

This study was supported by a grant of the Korea Health 21 R & D Project, Ministry of Health & Welfare, R. O. K (03-PJ10-PG13-GD01-0002)

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for the last 2 months and visited the outpatient clinic. Physical examination of this woman showed a blood pressure of 110/68 mmHg, a heart rate of 76 beats/min, and normal body temperature. Her body weight was 45.2 kg and she was 156 cm in height. Initial laboratory results were unremarkable with a normal PT of 13.5 sec (INR 1.03). Cardiomegaly was found on chest X-ray. Echocardiogram indicated atrial fibrillation. Echocardiogram also revealed decreased systolic function and hypertrophy of the left ventricle. The patient was started on 4 mg of warfarin daily to prevent thromboembolism.

When she revisited the outpatient clinic after 1 week, her PT was found to be 88.2 sec (INR 6.36) (Fig. 1). On admission to the ward, 10 mg of Vitamin K was injected with warfarin withdrawal. After normalization of the patient's PT, 2 mg/day of warfarin was initially prescribed and the dose was then increased to 3 mg/day, which resulted in a PT of 36.3 - 47.0 sec (INR 2.69 - 3.45). Administration of warfarin doses was reduced even further (1 - 2 mg/day) to achieve the target therapeutic INR of 2.0 to 3.0 and she was discharged after 16 days of hospitalization. She continues to

receive warfarin therapy at the outpatient clinic monthly and her PT remains stable, even though her warfarin dose has been reduced to 2 mg/day.

This patient was genotyped for *CYP2C9*. DNA was isolated from peripheral blood and all 9 exons of *CYP2C9* gene were amplified by PCR.¹¹⁻¹³ The PCR products were sequenced using ABI PRISM BigDye terminator Cycle sequencing kit (Perkin-Elmer, USA) and an ABI Prism 3100 Genetic Analyzer (Perkin-Elmer, USA). The patient was an intermediate metabolizer with the genotype of *CYP2C9**1/*3 (Fig. 2).

DISCUSSION

CYP2C9, one of the major isoforms of the *CYP2C* subfamily, is involved in the metabolism of many clinically important therapeutic agents such as warfarin, phenytoin, sulfonylurea and nonsteroidal anti-inflammatory drugs.^{1,11} Genetic polymorphisms of *CYP2C9* bring about significant variability among individuals in drug response.

At the time of this report,¹² variant alleles of *CYP2C9* had been reported.¹⁴ Previous studies have demonstrated that 2 common variants *CYP2C9**2 and *CYP2C9**3 are associated with reduced catalytic activity of *CYP2C9*.¹⁻¹¹ Therefore, subjects who are homo- or heterozygous for these variant alleles require reduced maintenance doses for *CYP2C9* substrates including warfarin. The *CYP2C9**3 variant would have a greater impact than the *CYP2C9**2 variant on the dose requirements of warfarin.^{2,3,11} Intermediate metabolizers with heterozygous *CYP2C9**2 and *CYP2C9**3 would require on average 21% and 34% lower maintenance doses of warfarin, as compared with extensive metabolizers (*CYP2C9**1/*1).² Poor metabolizers with 2 variant alleles (*CYP2C9**2/*2, *CYP2C9**2/*3 and *CYP2C9**3/*3) would require 60 - 90% lower doses of warfarin than extensive metabolizers.^{2,3,11}

Allele frequencies of *CYP2C9* variants have been shown to be markedly different among populations. Caucasians possess higher frequencies of *CYP2C9**3 than Asians (6-10% vs 2-5%).¹⁻³ 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

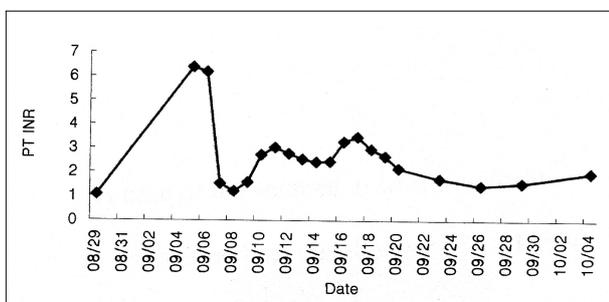


Fig. 1. Time course of warfarin therapy and international normalization ratio of prothrombin time.

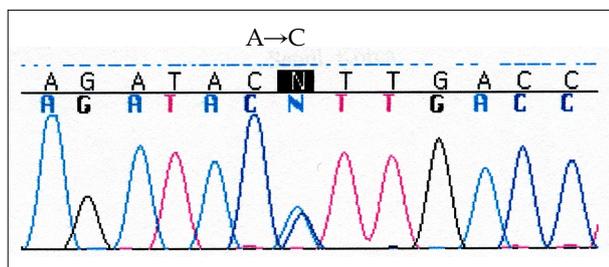


Fig. 2. Detection of nucleotide changes by sequencing analysis of *CYP2C9* gene in the individual heterozygous for the *CYP2C9**3 allele with A1075C (Ile359Leu) substitution.

Yoon et al reported that from a pool of 574 Koreans 2.3% were heterozygous for CYP2C9*3 and none were found to be carriers of CYP2C9*2.¹⁵ Interethnic difference in the prevalence of CYP2C9 variants causes an apparent need for an interethnic difference in the maintenance dose of warfarin.⁹

There are several Korean reports¹⁶⁻¹⁸ regarding warfarin dosing and its toxicity based on clinical assessment and PT monitoring. This case study is the first clinical report of a Korean patient with the CYP2C9*1/*3 genotype as the major determinant of warfarin intolerance. She attained an extremely high INR at the standard doses and might be at a higher risk for developing severe complications. In this patient, we could not identify any specific pharmacokinetic or pharmacodynamic factors associated with warfarin response, such as drug interactions or disease conditions. Therefore, a pharmacogenetic test was performed to explore the possible genetic factors contributing to the unusual drug response. This patient could have taken appropriate therapeutic changes earlier and been maintained on a safer regimen with lower doses, if she had been genotyped at the beginning of warfarin therapy.

The CYP2C9 genotype is associated with a risk of over-anticoagulation and bleeding complications. Previous studies have suggested that the variant group, compared with patients with the wild-type genotype, required a higher rate of above-range INR, more time to therapeutic INR, larger maintenance doses, more time to stable warfarin dosing, longer hospitalization, and a higher risk of serious bleeding events.^{1-4,6,7,11}

At present, clinicians are used to adjusting the warfarin dose based on PT and clinical response. Additional CYP2C9 genotyping can serve as an important guide for more rapid dosage adjustment and prediction of drug response in each individual. CYP2C9 genotyping is recommended to complement PT monitoring especially when the unusual metabolic capacity of warfarin is suspected. Characterization of CYP2C9 polymorphic alleles may identify patients at risk, so that warfarin can be given more cautiously, especially during the induction phase of anticoagulation.

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