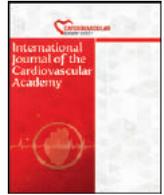




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## Case report

## Genetic warfarin resistance in a patient with mechanical prosthetic aortic valve☆

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## ABSTRACT

Warfarin resistance is a rare but an important clinical problem in patients requiring anticoagulation. Here we report a male patient with a mechanical aortic prosthetic valve who did not have a target level of therapeutic anticoagulation on warfarin. A pharmaco-genetic testing revealed VKORC1 A/G and CYP2C9 \*1\*1 genotype. His prothrombin time level with international normalization ratio (INR) was 1–1.3 on warfarin 80 mg per day. Phenprocoumon was not successful to increase INR level. He has been given enoxaparine BID (1 mg/kg) without any thromboembolic events at follow-up. Although VKORC1 and CYP2C9 genes are two major genetic factors responsible for this clinical situation, more studies seem to be necessary to explain this phenomenon.

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## Introduction

Warfarin is a widely used oral anticoagulant with a narrow therapeutic window and high inter-individual variability. Patients require different dosages of warfarin for a target international normalization ratio (INR) level, but 95% of them need more than 1 and less than 9 mg. Patients requiring 9 mg or more warfarin are therefore classified as warfarin-resistant.<sup>1</sup>

## Case report

The subject is a 35-year-old male patient with mechanical aortic prosthetic valve. After surgery, his warfarin dose is gradually increased to 80 mg daily since an optimal INR level is not achieved at usual dosages. Accordingly, we thought the patient had warfarin resistance. We investigated possible causes of acquired resistance. He is compliant with the therapy and taked no concurrent medications which interact with warfarin. He had no gastrointestinal disorders. His diet did not contain excessive amount of vitamin K. His anticoagulant switched to phenprocoumon which has longer half-life than warfarin. However, the patient did not have targeted INR levels. He is started enoxaparine twice daily (1 mg/kg) therapy. He experienced no thromboembolic events.

Warfarin resistance can be either acquired or hereditary. Possible causes of acquired resistance include enzymatic induction of warfarin

metabolism by other drugs, enhanced dietary intake of vitamin K, non-compliance with therapy and hypothyroidism.<sup>2</sup>

Genetic factors are contemplated to play role in determining optimum dose for an individual. Studies have demonstrated the effect of CYP2C9 (cytochrome P450) and VKORC1 (vitamin K epoxide reductase complex) gene polymorphisms on the dosages of oral coumarin anticoagulants. Cytochrome P450 2C9 enzyme is involved in the elimination of warfarin. Allelic variants of CYP2C9 gene, CYP2C9\*2(Arg144Cys) and CYP2C9\*3 (Ile359Leu), have less catalytic activity than the wild type CYP2C9\*1(Arg144/Ile359). The presence of these variants in an individual is thus expected to lower the requirements of the drug.<sup>3</sup>

Several years ago, VKORC1 has been identified as the gene encoding vitamin K epoxide reductase (VKOR) - the target protein for coumarin derivatives like warfarin or phenprocoumon.<sup>4</sup> The vitamin K oxidoreductase (VKOR) is an integral membrane protein that reduces vitamin K to support the carboxylation and consequent activation of vitamin K-dependent proteins.<sup>5</sup> Heterozygous VKORC1 missense mutations have been identified in individuals who are resistant to warfarin and homozygous mutations have been reported in families with combined deficiency of vitamin-K-dependent clotting factors type 2 (MIM 607473). VKORC1 missense mutations alter vitamin-K epoxide reductase activity and, therefore, play a considerable role in the warfarin-resistant phenotype.<sup>6</sup>

Patients with G allele for VKORC1-1639G>A have a significantly higher number of thromboembolic complications per month during therapy. VKORC1-1639G>A, age, CYP2C9\*3, and smoking status explain 43.4% of the overall variability in the warfarin dose.<sup>7</sup>

In recent years, Ozer et al. have studied the impact of CYP2C9 and VKORC1 genetic polymorphism on warfarin dose requirements in adult Turkish population. The mean warfarin daily dose requirement was higher in CYP2C9 homozygous wild-type patients, compared to

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those with the variant \*3 allele ( $P < 0.05$ ), similar to those with the variant \*2 allele and highest in patients with the VKORC1-1639 GG genotype compared to those with the GA genotype and the AA genotype. The time to therapeutic INR was longer in CYP2C9 homozygous wild-type patients compared with those with the variant \*2 and \*3 alleles, and longer in patients with the VKORC1 (position – 1639) GG genotype compared with those with the GA genotype and the AA genotype.<sup>8</sup>

In the present case, pharmacogenetic testing revealed that our patient carried VKORC1 A/G variant and CYP2C9 \*1\*1 wild type. This genotype is expected to require higher doses of warfarin for adequate anticoagulation. Despite increasing warfarin doses over ranges in dose-prediction algorithms, the patient did not reach a target INR level of 2 to 3. His INR levels remained between 1.0 and 1.3, quite under therapeutic levels. His anticoagulant was switched to phenprocoumon, which has a longer half-life than warfarin. It did not increase INR levels either. Therefore, he is currently being treated with enoxaparine twice daily. He has experienced no thromboembolic events so far.

In patients requiring high dose warfarin for target anticoagulant effect, polymorphisms of VKORC1 and CYP2C9 genes should be considered and they should be investigated. Alternative anticoagulant agents like enoxaparine can be used in such patients.

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