

# Warfarin Resistance: A Case Report

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## Abstract

Warfarin is the most widely prescribed anticoagulant in the world. Patients who need more than 15 mg per day should be considered warfarin-resistant. Nearly 30 genes have been reported in association with warfarin pharmacogenetics but genetic polymorphisms in the genes encoding CYP2C9 and VKORC1 have been shown to act as the most important determinants of drug dosage requirements. The major enzyme responsible for the metabolism of S-warfarin, the more potent of warfarin's two stereoisomers, is CYP2C9. Warfarin inhibits vitamin K epoxide reductase (VKOR). A 30-year-old woman was referred to our clinic for pulmonary embolism. She was treated with low molecular weight heparin. The warfarin dose was titrated up to 15 mg daily but after one week, the INR (international normalized ratio) was still subtherapeutic level at 1.8. In this paper, we discuss underlying genetic polymorphisms about warfarin resistance.

**Keywords:** Warfarin, vitamin K epoxide reductases, VKORC1

## Introduction

An outbreak was observed cattle in the Northern USA and Canada in the 1920s. The disease was characterised by fatal bleeding, either spontaneously or from minor injuries. Nearly 20 years later, Karl Link discovered that the anticoagulant in sweet clover was 3,3'-methylenebis (4-hydroxy coumarin). Further work by Link led in 1948 to the synthesis of warfarin. The name warfarin is derived from the sponsor (Wisconsin Alumni Research Foundation) and -arin from coumarin (1).

The glutamate residues in some coagulation factors (II, VII, IX, X) are carboxylated in presence of O<sub>2</sub>, CO<sub>2</sub>, and the enzyme carboxylase, to form γ- carboxylglutamate (Gla) residues. Vitamin K is essential for this post translational modification in the liver. In this process, vitamin K hydroquinone converted to vitamin K epoxide. Then, vitamin K epoxide reductase (VKOR) turned its epoxide to vitamin K again. Warfarin exerts its anticoagulant effect by inhibiting (2) the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1).

The frequency of referral of patients with warfarin related complications to the emergency unit increases (3). The patients with warfarin resistance can present atypical chest pain due to pulmonary emboli (4,5). Intracardiac thrombi can develop during warfarin therapy in such cases (6). Warfarin resistance defined as warfarin requirements greater than 15 mg per day to maintain the international normalised ratio (INR) in the target therapeutic range (7). We present a patient with warfarin resistance who had related mutations.

## Case Report

A 30-year-old woman was admitted to the outpatient clinic of chest department of the city hospital for chest pain. Her medical history was unremarkable. Chest computed tomography (CT)-angiogram was consistent with pulmonary embolism. The patient's initial treatment was low-molecular-weight heparin. A loading dose of warfarin 5 mg daily was started at the second day of admission. The warfarin dose was titrated up to 15 mg daily for one week, the INR was still subtherapeutic at 1.8. She did not



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report any dietary changes or other drug intake. We performed genetical analyses to explain warfarin resistance. Warfarin therapy was stopped and low-molecular-weight heparin was started again.

Real time technique was used in the genotype analysis of target genes in current proband patient. Total genomic DNA was extracted from peripheral blood sample from patient with spin column extraction technique (Roche). *SERPINC1* gene was sequenced with Genetic analyser (ABI Prism 3130, Germany) and target thrombophilia genes of factor V Leiden, factor II, *MTHFR* C677T and A1298G, PAI1, exon 7 of *CYP2C9\*2\*3* (rs1057910) and promoter region of *VKORC1* (rs9923231) were amplified by using real-time PCR technique (LightCycler 2.0, Roche). Case was intermediate metabolising profile for the *CYP2C9* gene (*CYP2C9\*1/\*2*), Both SNPs (C677T and A1298C) were also in heterozygous mutated profile for target *MTHFR* gene. Heterozygous point mutation was detected in *VKORC1* -1639>A allele in the current proband case with warfarin resistance. The rest of genes that analysed (factor V Leiden, factor II, PAI-1 and *SERPINC1*) were in normal structure.

## Discussion

It has been shown that methylenetetrahydrofolate reductase C677T and A1298C, plasminogen activator inhibitor-1(PAI-1) 4G/5G mutations were associated with an increased risk of deep venous thrombosis (8). We did not find any other predisposing factors related to pulmonary embolism in our case.

Combining age and body surface area together with genetic polymorphisms in *CYP2C9* and *VKORC1* accounted for 55% of the variance in dosage requirements (1). The daily warfarin doses of patients with the *CYP2C9\*1/\*2* were not significantly different from those of patients with the wild-type (*CYP2C9\*1/\*1*) mutation in Turkish population (9). Consequently, we suggested that *CYP2C9\*1/\*2* mutation found in our patient did not contribute to warfarin resistance.

In Turkish patients, *VKORC1*-1639 G>A polymorphism found approximately 15% of the inter-individual variability in the warfarin dose requirement as the largest contribution (9). Mean dose was reported as 5 mg in wild-type GG mutation but 3.5 mg in the heterozygous (AG) group. Because our patient had heterozygous mutation, we cannot explain warfarin resistance via this mechanism. In Turkey, it has been shown that GG mutation had a higher dosage requirement for warfarin compared with the other genotypes (10). On the other hand, in Chinese population, warfarin maintenance doses in AG + GG carriers were higher than those in AA carriers (11).

D'Andrea et al. (12) reported that the mean dose of warfarin was higher (6.2 mg) among Caucasian patients with the *VKORC1* 1173CC genotype than those of patients carrying the CT (4.8 mg) or the TT genotype (3.5 mg). In Chinese patients, warfarin dose was apparently higher in patients with CT genotype (3.8 mg) as compared with patients with TT genotype (3.1 mg). There is no study about *VKORC1* 1173 genotyping in Turkish patients. Turkish society is composed of people of many different ethnic backgrounds such as Turkish, Asian, and Caucasian.

The *in vitro* analysis revealed that only six mutations of the *VKORC1* (A26P, A41S, V54L, H68Y, I123N and Y139H) have been found to be associated with warfarin resistance among more than 26 missense mutations (2). Our study has limitation because of the absence of investigations for constitutional mutations of *VKORC1*. We could perform only *VKORC1* promoter G-1639A and first intron C1173T polymorphisms genotyping in our patient.

## Conclusion

In conclusions, warfarin resistance in the present case was still unknown. We continued low-molecular-weight heparin in our patient. Ethnic difference is important because of other genes and other rare polymorphisms affect warfarine metabolism. In addition to *CYP2C9* and *VKORC1*, polymorphisms in other genes that may help determine the dose of warfarin should be investigated.

## Ethics

**Informed Consent:** It was taken.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: U.G., T.G., Concept: U.G., T.G., Design: U.G., T.G., F.S., Ö.Ö., Data Collection or Processing: U.G., T.G., Analysis or Interpretation: U.G., T.G., Literature Search: U.G., T.G., Writing: U.G., T.G., F.S., Ö.Ö.

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