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*CYP2C9*1*2* and *VKORC1-1639 AA* Polymorphisms Correlation with Warfarin Dose Requirement: A Case Report

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CYP2C9 and *VKORC1-1639 G>A* genes as the genetic factors significantly influence the warfarin dose requirement in individuals. The patients with genetic variations in CYP2C9 and VKORC1 are at increased risk of adverse warfarin-related events. A young patient with atrial septal defect being highly sensitive to normal daily dose of warfarin was subjected to the study. The patient consented to genetic testing. Furthermore, DNA was isolated and PCR-RFLP performed. The patient required low warfarin dose of 11 mg/week to achieve the target international normalized ratio (INR). Genetic testing revealed that the patient carried VKORC1-*1639 AA* and *CYP2C9*1*2* genotypes. Our findings reaffirm the significance of pharmacogenetic analysis prior to the warfarin therapy to achieve an efficient treatment and the least side/adverse drug effects.

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Introduction

Warfarin is an anticoagulant drug which minimizes the thromboembolic risk[1, 2]. To get to the target international normalized ratio (INR), response to a steady-state dose of warfarin varies from one patient to another. Due to the high risk of bleeding, it is extremely important to identify the patient's sensitivity before starting warfarin therapy [3, 4].

This sensitivity has been proved to correlate with the genetic polymorphism of *CYP2C9* and *VKORC1* whichaffects the required dose of warfarin [5]. The present study reports a case with *VKORC1-1639 AA* and *CYP2C9*1*2* genotypes with very low threshold for warfarin tolerance.

Case Presentation

This study was approved by Ethical Committee of Kermanshah University of Medical Sciences.In Kermanshah, Iran, a 21 years-old young adult (weight= 63 kg, and height =177 cm) was diagnosed with a large secundum atrial septal defect (ASD)who underwent transcatheter ASD closure. After surgery, he was prescribed with aspirin 25 mg PO daily, propranolol 10 mg PO daily, prednisolone 5 mg PO daily and cephalexin 500 mg PO daily. Also, heparin 500 IU was ordered for only 6 days and then discontinued and exchanged by warfarin. The initial warfarin dose was 3-4 mg/day to prevent thromboembolism. Ten days after surgery, the patient was discharged from the hospital with an INR of 3 and taking 4 mg/day of warfarin. The prothrombintime (PT) test was performed every week to control the INR. Four dayspostoperatively, the patient suffered frompostoperative complications, including insomnia and a slight fever (38 °C). Subsequently, the patient was admitted to the hospital and a chest x-ray photograph and an echocardiography (Echo) test was done. Immediately after, the left anterolateral thoracotomy operation was performed, and a 2.5 cm opening was made in the pericardium to drain the fluid accumulated around the heart. The drain was connected to the patient for 13 days. After this period, the fluid around the heart was considerably decreased, the drain was removed, and the patient was discharged. When the INR reached 3.8, warfarin (21 mg/day) was prescribed.

Following the INR test results, warfarin dose was reduced to 13 mg/week. After a week, INR was decreased to 2. The warfarin dose was increased again to 15 mg/week that resulted in the INR of 2.3 after four days. Warfarin 15 mg/week was prescribed for two months.

The patient consented to genetic testing. DNA was isolated and PCR-RFLP performed which revealed that the patient carried *CYP2C9*1*2* and *VKORC1-1639 AA* variants. Since the patients with *CYP2C9*1*2* and *VKORC1-AA* variants are expected to be warfarin sensitive, anticoagulant therapy was continued with warfarin 11 mg/week. Fifty days after treatment, PT test was done and INR found to be 1.84.

Discussion

CYP2C9 is the main enzyme in warfarin metabolism with one wild-type allele, *CYP2C9*1,* and two polymorphic versions, *CYP2C9*2* and *CYP2C9*3*. The polymorphic alleles reduce the warfarin metabolism compared to the wild type. Thus, to meet the target INR, a lower dose of warfarin is required [1, 4, 6]. The Vitamin K epoxide reductase (VKORC1) enzyme converts vitamin K into its different form assisting in activation of clotting proteins. Warfarin acts through inhibiting VKORCI [7]. Polymorphisms in *CYP2C9* and *VKORC1* genes are associated with variability of warfarin dose response among individuals. People with genetic variants of *CYP2C9* and *VKORC1* require lower warfarin dose to reach the target INR [8, 9]. Based on warfarin sensitivity, people are divided into several categories (Table 1) [2]. In wild-type subjects, the maintenance dose is 28-42 mg/week [10], while our reported case required extremely low doses of warfarin (11 mg/ week) to meet the target INR. In our case report, the patient with a high INR and low doses of warfarin was at increased risk of bleeding and also increased secretions associated with postoperative complications. Thus, in order to be maintained on more appropriate and safer regiment of warfarin according to his age, gender, weight, and concomitant drug therapy, the patient was

monitored regarding the genetic sensitivity to warfarin before continuing warfarin therapy. The patient reached the target INR of 1.8 with the warfarin dose of 11 mg/week.

In conclusion, the patients with *VKORC1-1639* AA and *CYP2C9*1*2* genotypes show high sensitivity to warfarin and the genetic testing for such patients is therefore necessary to minimize the adverse drug reactions and preventsevere complications.

Table 1. Sensitivity to warfarin based on combined *CYP2C9* and *VKORC1* genotyping.

Warfarin sensitivity	CYP2C9 genotype	VKORC1 genotype
Normal	*1/*1	G/A
Less than normal	*1/*1, *1/*2	G/G
Mild	*1/*3,*2/*2, *2/*3	G/G
	*1/*2	G/A
Moderate	*1/*1	A/A
	*1/*3,*2/*2	G/A
	*3/*3	G/G
High	*1/*2,*2/*2	A/A
	*2/*2, *3/*3	G/A
Very high	*1/*2,*2/*3,*3/*3	A/A

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Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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