CRCP Case Reports in Clinical Practice

Case Report

Journal Homepage: http://crcp.tums.ac.ir

Warfarin Resistance and Recurrent Thrombosis in an Iranian Patient

Masuod Malekzadeh[1], Marzieh Pazoki[2*]

1. Digestive Disease Research Center Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
2. Department of Pulmonary and Critical Care Medicine, Sina Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

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Citation: Malekzadeh M, Pazoki M. Warfarin Resisance and Recurrent Thrombosis in an Iranian Patient. Case Reports in Clinical Practice .2018; 3(3):90-93.

Running Title: Warfarin Resistance

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Article info:
Received: 28 July 2018
Revised: 22 August 2018
Accepted: 20 September 2018

Keywords:
Warfarin resistance; Iran

ABSTRACT

Warfarin resistance was known as subtherapeutic INR (International Normalized Ratio) in spite of normally prescribed doses of warfarin. There are few reports of warfarin resistance from Iran. In this article, we report a 43-year-old man with a history of deep vein thrombosis who took 10 mg of warfarin and 120 mg of enoxaparin daily. He was presented with new acute deep vein thrombosis while taking anticoagulants. Despite warfarin dose increase to 50 mg, the INR did not achieve the therapeutic level. His genetic testing was negative for *VKORC1* mutation but positive for *CYP2C9*3*, which proposed other underlying mechanisms for his warfarin resistance. This report added to the cases of warfarin resistance in Iran and herald more attention to warfarin metabolism and its interaction. Also it calls for checking serum warfarin level and Factor II and Factor X level for better evaluating compliance in patients presented with warfarin resistance.

Introduction

Warfarin resistance was known as subtherapeutic INR (International Normalized Ratio) in spite of normally prescribed doses of warfarin [1]. There are many reported cases of warfarin resistance [2-5]. Different factors such as diet, drugs and genetic background affect patient's response to warfarin [1, 6]. There are few reports of warfarin resistance from Iran [7, 8]. In this article, we report a patient with recurrent deep vein thrombosis with warfarin resistance and discuss possible underlying mechanisms and different solutions.

*** Corresponding Author:**
Marzieh Pazoki, MD.
Address: *Department of Pulmonary and Critical Care Medicine, Sina Medical Center, Tehran University of Medical Sciences, Tehran, Iran.*
E-mail: *asapazoki@gmail.com*

Case Presentation

A 43-year-old man was presented with left leg swelling and edema 5 months before referring to our clinic. After confirming diagnosis of Deep Vein Thrombosis (DVT) on Doppler sonography, he underwent anticoagulation. However, his INR remained in subtherapeutic level, even after increasing warfarin dose to 10 mg. Therefore, enoxaparin 60 mg BID was added to his regimen. While on this treatment, he had recurrence of pain and swelling in his left lower limb and was referred to our center. He underwent Color Doppler sonography again which showed acute DVT in his left leg. Therefore, warfarin dose was increased 2.5 mg every 3-5 days and enoxaparin dose was increased to 80 mg BID (patient weight was 80 kg).

After 12 days of admission, while receiving 20 mg warfarin per day, his INR was 1.32. He was scheduled to increase the warfarin dose in outpatient setting and checking INR every 3 days. Also prednisolone 15 mg daily was started for him in order to suppress any underlying immune process. After 14 days of taking prednisolone and receiving warfarin (30 mg daily), his INR was 1.3. Therefore, prednisolone was stopped and the patient was advised to continue increasing the warfarin dose every 3 days. Unfortunately, after taking 50 mg of warfarin per day, his INR was 1 (Table 1). Finally, because the patient was complaining from leg swelling and pain, we decided to start dabigatran (150 mg BID) instead of making further increase in warfarin dose. The patient took dabigatran for a week and his symptoms got much better.

Our patient was also tested for known polymorphisms of warfarin metabolism. He was negative for *VKORC1* mutation but positive for *CYP2C9*3* polymorphism. He also was found to have high TSH, normal T4 level, and positive anti-TPO, therefore levothyroxine was started for him. Other patient's laboratory findings are presented in Table 2.

Table 1. Patient's INR and corresponding warfarin dose

Date	Warfarin Dose (mg)	INR	Other Anticoagulants	Further Explanations
Oct 31, 2015	5	1.6		
Nov 15, 2015	5	1.1		
Dec 28, 2015	5	1.1		
Jan 4, 2016	7.5	1.1		
Jan 15, 2016	10	1.2		
Jan 26, 2016	10	1.05		
Feb 12, 2016	10	1.23	Enoxaparin 60 mg BID	
Feb 15, 2016	10	1.1		
Feb 20, 2016	12.5	1		Treatment in our clinic
Feb 27, 2016	15	1.21		
Mar 3, 2016	20	1.32		
Mar 8, 2016	20	2		
Mar 11, 2016	25	1.7		Prednisolone 15 mg daily was started
Mar 17, 2016	30	1.3	Enoxaparin 80 mg BID	
Mar 20, 2016	35	1.13		
Mar 23, 2016	40	1.2		Prednisolone was hold
Mar 27, 2016	45	1.1		
Mar 30, 2016	50	1		Dabigatran was started

Abbreviations: INR: International Normalized Ratio; and GI: Gastrointestinal

Table 2. Patient's other laboratory data on admission

Lab Test	Values	Lab Test	Values
WBC	4700(Neutrophils:51%)	Urea	22
Hb	15	Cr	1
MCV	99	CRP	4.5
Plt	166	ESR	15
Na	138	Anti-dsDNA	10.9
K	4.06	ANA	0.6
PTT	32	Anti-cardiolipin Ab IgM	1.5(>7)
PT	134	Anti-cardiolipin Ab IgG	5(>10)
INR	1	Anti B2 Glycoprotein I	3.5(>8)
TSH	13.69(0.3-3.5)	C3	158(83-177)
T4	4.7	C4	39(15-45)
T3	1.5	CH50	90(70-150)
Anti-TPO	461(<30)	U/A	RBC=13-14

Abbreviations: WBC: White Blood Cell; Hb: Hemoglobin; MCV: Mean Corpuscular Volume; Plt: Platelet; Cr: Creatinine; PTT: Partial Thromboplastin Time; PT: Prothrombin Time; INR: International Normalized Ratio; U/A: Urine-Analysis; ESR: Estimated Sedimentation Rate; CRP: C-Reactive Protein; TSH: Thyroid Stimulating Hormone; and TPO: Thyroid Peroxidase Antibody.

Discussion

In this article, we reported a case of warfarin resistance. Warfarin resistance should be sought if the patient has subtherapeutic INR in spite of taking 15 mg warfarin per day [1]. First we evaluated patient's compliance. We asked patient's companion about his compliance and became sure that he took warfarin regularly. Accordingly, we reviewed patient's medication and diet again. He took methadone which has not been reported to interfere with warfarin.

There were few reports of warfarin-tramadol interaction [9-11] which consistently showed elevated INR in those tanking tramadol. The same but smaller effect was also noted for morphine-warfarin interaction [11]. However, to the best of our knowledge there were no report of methadone-warfarin interaction in literature and considering that methadone is in the same drug category with morphine and tramadol, we would expect methadone, if interact with warfarin, to elevate INR with lower dose of warfarin. We also prescribed levothyroxine for him.

It was shown that levothyroxine has no significant interaction with warfarin [12], confirming that patient's drugs had no interference with anticoagulation. The patient also had regular consumption of citrus (tangerine and oranges) before and during admission. Although taking high doses (1000 mg daily) of vitamin C causes warfarin resistance [4], the daily dose of vitamin C in 3-4 oranges or tangerines (about 200 mg vitamin C) is not of matter. However, the patient was advised to reduce amount of daily citrus intake.

Our patient's genetic testing was negative for *VKORC1* mutation and positive for *CYP2C9*3* polymorphism. *CYP2C9* polymorphism was known to cause less warfarin metabolism and leads to warfarin sensitivity [1]. Although it was proposed by Kimmel et al. that *CYP2C9* prevalence is different in various ethnicities and may not be useful for specific racial group such as African American [13]. In one study in Iran, it was showed that *CYP2C9*3* leads to lower doses of warfarin for reaching therapeutic range of INR [14].

This report was in sharp contrast with our patient who had *CYP2C9*3* polymorphism and warfarin resistance. However, there was a similar report of warfarin resistance with similar genetic background from Japan [5]. This suggests that warfarin resistance in our patient may be due to other underlying mechanisms rather than *VKORC1* and *CYP2C9* mutations. In addition, the patient had INR more than 5 in the first few weeks of starting warfarin (Table 1) which highlighted the pos-

sibility of noncompliance more than underling genetic polymorphism. However, as checking serum levels of Factor II, Factor X and warfarin was not available and the patient was symptomatic we planned to change the anticoagulant from warfarin plus enoxaparin to a direct thrombin inhibitor (dabigatran). The patient's symptom was relieved substantially after starting dabigatran.

This report add to previous reported cases of warfarin resistance in Iran [7, 8] and herald more attention for physician about warfarin metabolism and its interaction. This report also calls for checking serum warfarin, Factor II, and Factor X level for better evaluating compliance in patients presented with warfarin resistance.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participant was informed about the purpose of the research and its implementation stages.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We appreciate Sina Hospital Research Development Center for helping us to complete this study.

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