Case Report

A Case of Unexplained Warfarin Resistance: A Case Report and Literature Review

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Abstract

Adjusting the exact warfarin dose has always been challenging since it has a narrow therapeutic window. Numerous factors, including poor drug compliance, drug-drug interactions, and malabsorption syndromes, affect the warfarin plasma concentration, leading to oversensitivity or resistance to warfarin. Patients who need more than 15 mg/d of warfarin for maintained anticoagulant effects are considered warfarin resistant.

We describe a 62-year-old man referred to our center with bruising on his feet in June 2021. The patient had a history of valve replacement (mechanical prosthetic valves in 2013), hypothyroidism, and atrial fibrillation. He presented with warfarin resistance (first noticed in 2013) and did not reach the desired warfarin therapeutic effect despite receiving 60 mg of warfarin daily.

Upon admission, the patient was on warfarin (100 mg/d) with an international normalized ratio (INR) of 1.5. He underwent laboratory and molecular genetic tests, which showed no mutation in the CYP2C9 and VKORC1, the genes associated with warfarin resistance.

A stepwise diagnosis is required to identify the underlying cause. Assessing the patient's compliance, drug history, dietary habits, malabsorption diseases, and genetics may be necessary. We evaluated these possible reasons for resistance and found no correlation. The patient's warfarin intake was monitored closely to reach the INR therapeutic target of 3-3.5. He decided to leave the hospital with personal consent. He was discharged with a cardiologist referral and 24 warfarin tablets daily (120 mg/d) with an INR of 1.8. The patient was followed up 6 months and 2 years after discharge and was on the same daily dose of warfarin as at discharge, with no complications.

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Introduction

Adjusting the exact dose of warfarin, a vitamin K antagonist (VKA), has always been challenging for healthcare providers since it has a narrow therapeutic window. Numerous factors affect the concentration of warfarin in blood and its anticoagulant effects. Some may lead to oversensitivity to and others to resistance to warfarin. As a definition, patients who need more than 15 mg/d of warfarin for the anticoagulant effects to be maintained are considered warfarin resistant.[1]

Poor drug compliance is the most common reason for warfarin resistance. Hence, patients exhibiting resistance should undergo examinations for adequate drug use.[2] Warfarin undergoes a vast number of drug-drug interactions. There are various mechanisms by which medications interact with VKAs. These mechanisms can result in a prolonged prothrombin time/international normalized ratio (PT/INR), an increased bleeding risk independent of PT/INR, and reduced anticoagulation.[3-6] Dietary factors also play a crucial role in modifying the warfarin effect.[7,8] Parenteral nutrition may also cause warfarin resistance.[9]

Hyperlipidemia requires more warfarin for desired effects.[10] Serum albumin levels interfere with warfarin: hypoalbuminemia increases the free portion of warfarin, enhancing its clearance, whereas hyperalbuminemia alters its plasma level by changing the concentration of other drugs. Both conditions result in warfarin resistance.[2] Warfarin is bound to several enteral feeding products, especially protein components, causing a reduction in warfarin bioavailability.[11]

We herein describe a patient with a history of valve replacement (mechanical prosthetic valves) and atrial fibrillation (AF) who showed warfarin resistance despite having normal routine genetic tests for the condition. The study protocol was approved by the Review Board of Rajaie Cardiovascular Medical and Research Center. The patient received comprehensive explanations about the research process and agreed to enroll by providing informed written consent. The study adhered to the Helsinki Statement.

Case report

The patient was a 62-year-old Caucasian man from Sari, Iran, who was referred to our center in June 2021 with a complaint of bruising on both feet and warfarin resistance. He was a known case of AF with a history of warfarin resistance, first noticed in 2013. The patient's resistance to warfarin was then linked to hypothyroidism, and he had taken levothyroxine ever since, with the warfarin dosage adjusted accordingly. The patient had a history of acute rheumatic fever in 1982 and underwent mitral commissurotomy in the same year. He also underwent concomitant atrial, mitral, and tricuspid valve replacements with mechanical prosthetic valves in 2013. In that admission, a coronary computed tomography angiography yielded normal results. His past medical and habitual history (eg, alcohol consumption and cigarette smoking) was unremarkable.

In the last admission just prior to referral to our center, the patient was hospitalized in Sari in May 2021 with bruised feet and an international normalized ratio (INR) below 1.8 despite receiving 12 warfarin tablets daily (60 mg). He did not present with signs and symptoms of anemia, gastrointestinal bleeding, and cerebrovascular accident. Echocardiography illustrated a fixed bileaflet tricuspid valve with a pressure gradient of 5 mm Hg, a mass (1×1.9 cm) on the tricuspid valve, moderate tricuspid transvalvular leakage with clot formation (1.3×1.13 cm), and normal pulmonary arterial pressure (27 mmHg). Fluoroscopy confirmed the echocardiographic findings. The patient was administered 80 mg of enoxaparin twice daily and a bolus of 10 international units (IU) of reteplase with a subsequent 10 IU reteplase infusion. His INR began to rise once the reteplase was started. Subsequently, the treatment was bridged to warfarin with a view to maintaining INR. The patient was discharged with 20 warfarin tablets daily (100 mg/d) with an INR of 1.5. Afterward, he was referred to our center for further workup on warfarin resistance.

Upon admission to our center, in addition to warfarin (100 mg/d), the patient had been on levothyroxine (100 µg once daily) for at least the preceding 3 months and was euthyroid. His drug history was otherwise negative. ECG Holter monitoring and laboratory and molecular genetic tests were carried out. The 24-hour ECG Holter monitoring was compatible with AF and showed an average heart rate of 77 (minimum of 33 and maximum of 203) bpm. The diurnal and nocturnal heart rate averages were 81 and 69 bpm, respectively. RR instability was evident with minimum and maximum RR intervals of 235 milliseconds and 2150 milliseconds, respectively. In the monitoring period, 47 isolated and 1 couplet ventricular beats were observed, as well as 42 isolated and 9 couplet supraventricular ectopic beats. One episode of supraventricular tachycardia occurred with a heart rate of 175 bpm for 5 seconds. During the monitoring, the patient was asymptomatic. The overall interpretation was AF rhythm with a variable ventricular response.

The results of the routine laboratory tests were as follows: blood group: O positive; red blood cells: 4.05×10^{12}/l; white blood cells: 4.7×10^{9}/l; hemoglobin: 12.2 g/dL; hematocrit: 37.6%; erythrocyte sedimentation rate: 8 mm/h; C-reactive protein: 31 mg/mL; alanine transaminase: 38 U/l; aspartate transaminase: 43 U/l; creatinine: 1.2 mg/dL; potassium: 3.9 mmol/l; sodium: 133 mmol/l; thyroid stimulating hormone (TSH): 2.54 mIU/L (reference range = 0.35-4.99); T3: 0.7 µg/dL (reference range = 0.5-1.59); T4: 7.1 µg/dL (reference range = 4.87-11.7); stool occult blood: trace positive.

The molecular genetic testing for the patient comprised

DNA extraction via the salting-out method. A subsequent restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) analysis was performed to examine the single-nucleotide polymorphisms of the *CYP2C9* and *VKORC1* genes. The sensitivity and resistance tests detected no mutation. The results are shown in Table 1.

Table 1. Genetic test results of SNPs

SNP	Genotype
Sensitivity Testing	
CYP2C*2 (c. 430 C>T)	CC: no mutation detected (N/N)
CYP2C9*3 (c. 1075 A>C)	AA: no mutation detected (N/N)
VKORC1 (c. 1639 G>A)	GA: no mutation detected (N/N)
Resistance Testing	
VKORC1 (c. 106 G>T)	GG: no mutation detected (N/N)
VKORC1 (c. 196 G>A)	GG: no mutation detected (N/N)
VKORC1 (c. 383 T>G)	TT: no mutation detected (N/N)

SNP, Single-nucleotide polymorphism

In our center, the patient's warfarin intake was monitored until INR reached the therapeutic target (3-3.5). However, he decided to leave the hospital with personal consent and return to Sari. The patient was referred to a cardiologist in Sari for further INR monitoring and treatment continuation. He was given a discharge note containing a complete history, treatments, and prescriptions. He was discharged with 24 warfarin tablets daily (120 mg/d) with an INR of 1.8. The patient was followed up 6 months and 2 years after leaving the hospital and was on the same daily dose of warfarin as at discharge with no complications.

Discussion

The metabolism of warfarin can explain warfarin resistance. Warfarin has 2 enantiomers that are metabolized separately by cytochromes P450. *CYP1A2*, *CYP3A4*, and carbonyl reductase metabolize the R-warfarin to 6- and 8-hydroxy warfarin, 10-hydroxy warfarin, and diastereoisomeric alcohols, respectively. S-warfarin is metabolized primarily by *CYP2C9* to 7-hydroxy warfarin. The effect of warfarin is mainly altered when the metabolism of s-warfarin is changed.[12] Changes in the activity of these cytochrome p450 enzymes can affect the plasma level of warfarin. Given that these enzymes metabolize many other drugs, it is reasonable to expect broad drug interactions with warfarin. Additionally, genetic variations of these cytochrome complexes can be the reason for different sensitivity to warfarin. *CYP2C9*2* or *CYP2C9*3* variant alleles decrease enzyme activity and increase warfarin sensitivity. Polymorphisms of *CYP3A4* or *CYP1A2* may also cause warfarin sensitivity or resistance.[13] Polymorphism of the *VKORC1* gene can result in increased amounts of *VKORC1* protein or types with a reduced ability of warfarin to attach to and deactivate, causing warfarin resistance and vice versa. *VKORC1* Asp36Tyr and *VKORC1* p.D36Y mutations are associated with warfarin resistance,[14,15] while *VKORC1* 1639G>A mutation is related to warfarin sensitivity.[16]

To determine the cause of warfarin resistance, the first step is to evaluate the patient's adherence to the medication regimen. An accurate history of drugs, including over-the-counter medications, should be obtained, and any specific or unordinary dietary habits and a history of malabsorption syndrome should be enquired.[2,17]

In the absence of the above causes, measuring the plasma level of warfarin can be helpful. Studies suggest a therapeutic serum warfarin level of 0.5-3 μg/mL. Lower plasma levels of warfarin may indicate malabsorption problems after ruling out poor drug compliance or enhanced drug clearance due to possible pharmacokinetic resistance (eg, increased activity of related cytochrome p450s). Still, the therapeutic level of warfarin suggests pharmacodynamic resistance, which can be explained through the altered activity of *VKORC1* enzymes.[2]

Although not routinely advised, assessing factors II, VII, IX, and X activity levels might be beneficial. For instance, a 10-30% activity level of factors II and X is associated with the normal therapeutic effect of warfarin.[2]

To manage warfarin resistance, clinicians can analyze the plasma levels of warfarin and clotting factors II and X, in addition to employing pharmacogenetic analyses. An algorithm proposes investigating potential noncompliance, medication and dietary interference, and malabsorption disorders if the INR is less than 2.0 on a warfarin dose exceeding 15 mg/d. Checking factor II and factor X activity can reveal 2 options: (i) if the activity is below 40% of normal, the therapeutic warfarin dose may be unreliable, and the plasma warfarin level should be checked to confirm the diagnosis; (ii) if the activity is ≥ 40% of normal, pharmacokinetic or pharmacodynamic resistance may be suspected, and the plasma warfarin level should be checked. Therapeutic plasma warfarin levels suggest pharmacodynamic resistance, while subtherapeutic levels indicate pharmacokinetic resistance or noncompliance.[2]

Induction of hepatic *CYP2C9* (eg, rifampin, carbamazepine, phenytoin, and primidone) and bypassing the warfarin effect via large amounts of vitamin K (eg, some vitamin and calcium supplements) can lead to reduced anticoagulation.[3-6,18,19] One reason could be an external supply of vitamin K in these drugs, which can neutralize the effect of warfarin. In addition, other substances like ascorbic acid (vitamin C) are related to warfarin resistance.[20] Similarly, taking azathioprine, barbiturates, bosentan, carbamazepine, cholestyramine, cortisone, diuretics, haloperidol, mercaptopurine, nafcillin, oral contraceptives, pyrimidine, ribavirin, rifampin, ritonavir, spironolactone, and trazodone may decrease the warfarin effect.[2,8,21-23]

Medications that alter intestinal flora (eg, Cotrimoxazole, metronidazole, macrolides, and fluoroquinolones) inhibit hepatic cytochrome P450 2C9 (*CYP2C9*) (eg, fluconazole, voriconazole, valproic acid, fluoxetine, and amiodarone) and interrupt vitamin K recycling (eg, acetaminophen) and can lead to prolonged PT/INR, increasing the warfarin concentration and potentiating its effect. On the other hand, medications that interfere with platelet function (eg, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], and clopidogrel) or cause injury to gastrointestinal mucosa (eg, aspirin, NSAIDs) can increase the bleeding risk independent of PT/INR.[3-6]

Studies have shown the possible role of dietary factors interacting with VKAs. For instance, some vegetables like spinach, broccoli, and Brussels sprouts have high vitamin K content; hence, they are considered a highly probable cause of inhibiting the VKA effect. Conversely, several food items like cranberry, grapefruit, ginkgo, ginseng, mango, and alcohol are possible causes of augmented effects of VKAs.[7,8]

After the underlying cause is determined, a suitable strategy can confer the desired anticoagulant effect. The underlying cause should be eliminated if possible. Educating patients can increase their compliance and help them avoid drugs or foods that might interfere with the activity of warfarin. When there is pharmacokinetic or pharmacodynamic resistance, the clinician should consider increasing the warfarin dose and know that consuming over 100 mg daily might be indicated.[2] There have been previous instances of receiving 145 mg and 55 mg daily without any negative clinical effects, which supports this approach.[10,24] The dose can be titrated by genome testing and finding the responsible mutations.[2]

Using non-VKA anticoagulants like direct oral anticoagulants (DOACs) and direct thrombin inhibitors (DTI) or direct factor Xa inhibitors[2] and changing to other VKAs like Acenocoumarol may also be considered.[17] Sometimes, there are limitations to using a substitutional drug. For instance, despite several tests, standardized assays are not available for assessing the anticoagulant activity of new anticoagulants. Tests for classical anticoagulants are standardized, and therapeutic intervals are set using standards. However, standardization of tests used to evaluate new anticoagulants is lacking, making it challenging to translate their theoretical purpose into effective clinical activity.[25] Other drugs might not be available, or there might be circumstances where warfarin is the only indicated anticoagulant. For instance, VKAs are the only approved anticoagulants for preventing thromboembolic events after prosthetic valve implantation.[26,27] In a study, Dabigatran was associated with a higher rate of valve thrombosis in patients with prior prosthetic mitral valve replacement.[28] Such patients can be treated with higher doses of warfarin. Nonetheless, in some studies, change from a mechanical prosthetic to a bioprosthetic valve is reported to omit the need for warfarin.[1]

In the present case, our patient did not use any drug capable of decreasing the effect of warfarin, nor did he have any unusual dietary habits. He claimed proper medication adherence, which was also controlled by taking warfarin under the direct observation of healthcare providers while in the hospital. He did not have any history pointing to malabsorption syndromes. The analysis of *CYP2C9* and *VKORC1* gene polymorphisms showed no mutations. One explanation could be other possible mutations in the CYP complex and *VKORC1* genes rather than conventional ones that have been tested.

We ultimately planned to increase our patient's daily dose of warfarin intake to 120 mg to reach the desired therapeutic INR. Future studies should be conducted to weigh the benefits of titrating the dose of warfarin based on identifying the genetic reason for resistance against the approach in which an increased dose of warfarin is administered until the desired anticoagulant effect appears without knowing the causative mutation.

Conclusion

Further research is needed to identify the underlying mechanisms of warfarin resistance and improve patient outcomes. Future investigations should focus on genetic and environmental factors contributing to warfarin resistance. Genetic variations in the genes encoding *VKORC1*, *CYP2C9*, and *VKOR* have been associated with warfarin resistance, and further investigation of these genetic variations can help identify patients at risk of developing warfarin resistance and guide personalized dosing strategies. As mentioned earlier, environmental factors, such as diet and medication use, can also influence warfarin resistance, and research should investigate the impact of these factors on warfarin metabolism. Furthermore, investigations on epigenetic modifications and emerging technologies, such as pharmacogenomics, can provide novel insights into the molecular mechanisms of warfarin resistance and guide future drug development. Improving our understanding of warfarin resistance can improve patient outcomes and reduce the risk of adverse events associated with suboptimal anticoagulation.

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