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Case Report

A Man Who Takes 26 Warfarin Pills a Day! A Case Study on Warfarin Resistance

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ABSTRACT

In certain patients, particularly those receiving mechanical aortic valve replacement, warfarin is the sole permitted anticoagulant. Some individuals exhibit resistance to warfarin for a variety of reasons, necessitating extremely high and occasionally fatal doses of the medication for their survival. This report details a patient who demonstrates warfarin resistance and investigates the fundamental causes of this phenomenon. The case report emphasizes the possible role of genetic polymorphism in elucidating the mechanisms behind warfarin resistance.

Introduction

Warfarin obstructs the production of anticoagulants by hindering the carboxylation of vitamin K-dependent coagulation factors II, VII, IX, and X, thereby preventing blood clotting and thrombosis [1]. The effective prevention of thromboembolism is crucial for patients who have mechanical prosthetic heart valves. For this specific group, vitamin K antagonists (VKAs) continue to be the preferred medication, even with the increasing utilization of new anticoagulants for other medical conditions [2]. Due to its narrow therapeutic index, precise dosing and routine monitoring remain essential [3]. The therapeutic goal maintains an international normalized ratio (INR) in the range of 2.0–3.0 to optimize both efficacy and safety. The target INR is set at 3.0 for patients possessing a mechanical aortic prosthetic valve, excluding On-X valves, who present an additional risk factor for thromboembolic events. These risk factors include atrial fibrillation, a history of thromboembolism, left ventricular systolic dysfunction, or a hypercoagulable state. This target also extends to patients with older-generation mechanical aortic valve prostheses, such as ball-in-cage valves. Likewise, the target INR remains at 3.0 for patients with a mechanical mitral prosthetic valve, which includes the On-X valve, or for those with a mechanical tricuspid prosthetic valve [4]. When a patient necessitates high doses of warfarin (generally exceeding 20 mg per day, although certain sources classify resistance as requiring more than 70 mg per week (approximately 10 mg per day) or even over 105 mg per week (around 15 mg per day)), this situation is referred to as warfarin resistance, signifying an inadequate anticoagulation response [5]. Warfarin resistance can be classified into pharmacokinetic and pharmacodynamic mechanisms: Variants in CYP2C9 and other CYP450 enzymes affect the clearance of warfarin. Malabsorption syndromes may decrease the absorption of warfarin. A high intake of dietary vitamin K can negate the effects of warfarin. Drug-drug interactions, particularly with enzyme inducers like barbiturates, carbamazepine, and rifampin, can enhance warfarin clearance. Additionally, thyroid status plays a role, as hypothyroidism can diminish the action of warfarin [6].

A thorough assessment, which encompasses laboratory tests, a review of medications, an evaluation of dietary

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habits, and pharmacogenetic profiling, can uncover the root cause and guide the development of a customized management strategy aimed at maintaining a stable therapeutic INR while reducing potential risks.

We introduce a case involving a 54-year-old male patient who is a candidate for AVR, whose INR levels remained consistently below the therapeutic range despite continuous anticoagulant treatment. This case report highlights the potential impact of polymorphism in explaining warfarin resistance.

Case Report

A 54-year-old male who had received an aortic valve replacement (AVR) 19 years ago approached the Semnan Food and Drug Administration for a monthly allocation of 780 warfarin tablets. He required a daily dose of 130 mg of warfarin to maintain an INR level between 2.5 and 3 (Table 1). Over the course of these 19 years, he consistently needed warfarin doses exceeding 20 mg daily. Therefore, he was included in the group of warfarin-resistant patients. The patient had a prior diagnosis of hyperthyroidism, which was established around 18 months ago. He had two thyroid nodules, but after taking propylthiouracil (PTU), his thyroid status became euthyroid. He had initially been treated with methimazole, achieving partial remission. However, he subsequently experienced a relapse of thyrotoxicosis and is on PTU at a dose of 100 mg daily, alternating with 50 mg every other day, based on thyroid function monitoring (Table 1). In addition to his other medications, he was prescribed 40 mg of pantoprazole to be taken once daily and 2.5 mg of bisoprolol to be administered every 12 hours. The patient has consistently taken between 20 and 30 warfarin tablets daily for the past 19 years. He had never experienced any bleeding complications while using warfarin. There were no interactions between drugs and warfarin. Aside from the polymorphism category, no additional factors were considered regarding warfarin resistance; however, the patient was not willing to cooperate in undergoing polymorphism testing. Ultimately, following the inquiry made by the patient's physician regarding the quantity of warfarin requested, the Food and Drug Administration sanctioned a monthly allocation of 780 units of warfarin.

Discussion

Warfarin resistance is a complex condition influenced by multiple factors, necessitating an assessment of genetic predispositions, co-morbidities (such as thyroid disorders), lifestyle choices, and potential drug interactions [7]. Genetic polymorphisms serve as mediators of warfarin resistance. Two primary genes are recognized for their influence on warfarin efficacy: VKORC1 (Vitamin K epoxide reductase complex subunit 1): Variations, especially in the VKORC1 promoter region, may result in reduced sensitivity and/or heightened expression of the enzyme, thereby diminishing the effects of warfarin. CYP2C9 (Cytochrome P450 2C9): This enzyme in the liver is responsible for metabolizing the S-enantiomer of warfarin, which is the active form of the anticoagulant. Variants such as CYP2C9 modify the drug's metabolism, potentially impacting sensitivity and resistance based on the combination of alleles [8]. As warfarin functions by inhibiting clotting factors that depend on vitamin K, a significant intake of dietary vitamin K, particularly from green leafy vegetables such as spinach, may reduce its efficacy. An excessive consumption of foods high in vitamin K could result in INR levels that fall below therapeutic thresholds [9]. A range of medications can influence either the pharmacodynamics or pharmacokinetics of warfarin, consequently altering INR values: Hepatic enzyme inducers, such as phenytoin, may accelerate the metabolism of warfarin, resulting in decreased drug levels. Certain antibiotics can diminish the gut flora that produces vitamin K, thereby amplifying the effects of warfarin [9]. The function of the thyroid plays a crucial role in the metabolism of warfarin: Hyperthyroidism enhances the breakdown of clotting factors, leading to an increased sensitivity to warfarin. Consequently, lower doses of warfarin are typically sufficient. In contrast, hypothyroidism leads to a reduction in the breakdown of clotting factors, which can diminish the effectiveness of warfarin and mimic resistance, as previously noted. For these patients, achieving a therapeutic INR may necessitate the administration of higher doses of warfarin [10].

Table 1- Lab data results

Test	Result	Unit	Reference interval
PT	22.5	sec	0-12
Prothrombin activity	46	%	
INR	2.9	ratio	2.5-3.5
Creatinine	1.1	Mg/dl	0.4-1.6
TSH	0.45	miu/L	0.4-4.0
T4	10	Micg/dl	5.0-12.0

Conclusion

While instances of warfarin resistance are uncommon in the community and may necessitate elevated doses of warfarin, any increase in the warfarin dosage must adhere to established guidelines and involve ongoing monitoring of PT and INR levels. It is crucial to investigate the underlying causes of warfarin resistance. Should there be a suspicion of a polymorphism, examining the gene polymorphism as a potential factor contributing to warfarin resistance can prove beneficial.

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