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Interaction of warfarin with pomegranate juice in a patient with double valve replacement surgery: A case report

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Abstract

Warfarin is frequently used in the prophylaxis and treatment of various thromboembolic complications. However, its wide range of drug and food interactions, and narrow therapeutic index contributes to difficulty in its management. Therefore, it is important to highlight the relevance and significance of its interactions in the clinical settings. Interaction of warfarin with drugs are famous, however, little evidences are available for its interaction with food-items. We report a case of 51-year-old male operated for double valve replacement surgery, who was discharged with a 7-day follow-up with 5mg stable warfarin therapy and reported with significant increase in INR level after consumption of 480ml/day of pomegranate juice within 4 days of discharge. While this possible interaction needs to be further explored, clinicians should be aware of the relationship and properly interview their patients who are receiving warfarin and observe them closely.

Keywords: Warfarin-Pomegranate-Drug-Food Interaction-INR

Introduction

Warfarin was licensed in the United States in 1954 for human use and is indicated for both primary and secondary thromboembolic disease prevention. It is recommended in variety of conditions to prevent thromboembolic complications such as atrial fibrillation, pulmonary embolism, post-myocardial infarction, and after prosthetic valve replacement surgeries. Patients on warfarin therapy requires frequent blood tests to monitor the levels of prothrombin time and international normalized ratio (INR) [1].

Different factors, such as the small therapeutic range and its drug-food interactions lead to limitations in its use. Most warfarin patients will require a target INR range of 2 to 3 for therapeutic purposes. For patients with certain hypercoagulable disease states or with a mechanical heart valve, an alternative range of 2.5 to 3.5 is indicated. Warfarin is known to interfere with other medications and food items, which results in adverse outcomes. Hemorrhage in particular is a major concern when warfarin is used in conjunction with the other interacting agents. People with supra-therapeutic INR have a greater chance of hemorrhagic risks, including life-threatening gastrointestinal, intracerebral and other bleeding complications [2-3].

Warfarin metabolism occurs via cytochrome P450 enzyme system and several drugs and food substances that are subjected to cytochrome P450 metabolism thus interact with warfarin, ultimately leading to alteration in INR level. Warfarin consists of two enantiomers, namely R-warfarin and S-warfarin. R-warfarin is mainly metabolized by CYP1A2, CYP3A4 to 6- and 8-hydroxywarfarin, and 10-hydroxywarfarin respectively. S-warfarin is primarily metabolized by CYP2C9 to7-hydroxywarfarin [4]. Interactions between warfarin and food / medications exist with a wide variety of drugs metabolized by these P450s; however, warfarin's anticoagulant effectiveness is impaired mainly by altering S-warfarin metabolism via CYP2C9 [5].

The numerous drug–drug interactions that exist with warfarin are well documented. Less is known, however, about the potential interactions that may occur between warfarin and certain foods, especially fruits [6]. A few interactions showed well-described propensity towards anticoagulation with grapefruit juice by inhibition of CYP3A4 activity [7]. Three possible cases of association with cranberry juice were also reported [8]. It is important for both clinicians and patients to be aware of those substances that may interact with warfarin to avoid serious complications such as excessive bleeding and thrombosis due to suboptimal anticoagulation. In this case report we describe a potential case of interaction of warfarin with pomegranate juice leading to supra- therapeutic INR and coagulopathy in a 54 years old male after DVR surgery.

Case Report

A 51-year-old male patient with the history of mitral stenosis, aortic regurgitation, tricuspid regurgitation was operated for double valve replacement surgery (Mitral valve replacement + Aortic valve replacement), in Armed forces Institute of cardiology Rawalpindi Pakistan. He was discharged with drug therapy consisted of warfarin 5mg, digoxin 0.25mg once daily, sildenafil 25mg three times daily, famotidine 40mg once daily, cefixime 400mg Once daily, spironolactone 20mg Once daily. His INR level was 3.5 at the time

of discharge, which was within the therapeutic range. The patient was discharged with one week of follow up, and within 4 days after getting discharged patient was reported in anti-coagulation clinic with INR of 9.3 with no active bleed. Vitamin K 10mg Intravenous stats was given to the patient and he was admitted in the surgical ward for further treatment. His recent laboratory monitoring data included a lipid panel, hepatic panel, complete metabolic panel, and complete blood cell count. All results were within normal limits, except for mildly elevated creatinine level (1.4 mg/dl [normal range 0.84 to 1.21 mg/dl]) and alkaline phosphatase (122 U/L [normal range 35–104 U/L]) levels.

During his admission in the surgical ward, we reviewed the role of warfarin, goals of therapy, adverse effects, drug interactions, and diet interactions. The patient denied taking any other medication except the one, which were prescribed at the time of discharge. However, he stated that he had been consuming two glasses of pomegranate juice daily approximately 480ml day. We researched this information and found literature confirmation of potential warfarin-pomegranate juice interaction due to inhibition of cytochrome enzyme. No case study or literature study revealed that any other concomitant drug might cause this interaction. The patient was instructed to stop drinking the juice because of its potential interactions and the limited safety data.

Discussion

To our knowledge, two case reports have discussed the impact of pomegranate juice on warfarin, with limitations and lack of evidence in the studies. Nevertheless, there is literature on the possible association of pomegranate juice with other drugs and its effects on CYP metabolism. Pomegranate juice is famous due to its antioxidant and anti-atherosclerotic properties because of the high isoflavenoid content. It is becoming popular in cardiovascular diseases due to its potential health benefits [9].

The first case in 2009 speculated that INR dropped from 2.2-1.7 in a 64-year-old woman initially stabilized on warfarin therapy, after she stopped drinking pomegranate juice [10]. Even though her INR values seemed to stabilize after an increase in her warfarin dose, the author observed that the patient continued to have subtherapeutic INR values despite initial dose uptitration, and more dose adjustments were needed to sustain therapeutic INR levels. In this case, the possibility of an interaction between warfarin – pomegranate juice was less due to the need for continued warfarin dose adjustments after the patient had stopped drinking the pomegranate juice. It indicates other causes may have been responsible for the initial subtherapeutic INR, in addition to the cessation of pomegranate juice. In this scenario, it is unlikely whether there was a drug – food interaction.

The second case study outlined a 37-year-old woman, who was on chronic warfarin therapy and hospitalized due to higher INR level of 14, with large intramuscular hematoma formation after consuming 3 liters of pomegranate fruit juice during the previous week [11]. Using Drug Interaction Probability Scale, it was evaluated that in the patient there was a potential interaction between pomegranate juice and warfarin.

In this case study, interaction was based on the fact that this patient was discharged with well-controlled INR, and no other drugs were prescribed to the patient at the time of discharge, which could have potential interaction with warfarin, or being reported in literature or study [12]. Patient was afebrile and at the time of discharge, laboratory measurements such as creatinine, liver profile, albumin were in therapeutic range. Although the mechanism for this potential interaction is still not fully elucidated, however, laboratory experiments have shown that pomegranate juice interfere with warfarin metabolism by inhibiting cytochrome enzymes CYP3A4 and/or CYP2C9 and thus provides a mechanistic basis of this interaction, and pomegranate juice can also inhibit P-glycoprotein and thus increase the absorption of warfarin [13-14].

While two cases of warfarin – pomegranate juice interaction were reported, there were other variables in both of these studies that may have led to the irregular INR results and these cases certainly does not provided the absolute prove of warfarin and pomegranate interaction. In our case study, no other variable was present that could contribute to elevation in INR level. Therefore, we showed positive correlation between frequent pomegranate juice consumption of at least 480ml/day, which resulted in uncontrolled anticoagulation. This definitely proves the association between pomegranate juice consumption and increased bioactivity of warfarin as compared to previous case reports of drug interactions between pomegranate and warfarin.

Conclusion

This case report illustrates the significance of taking a full history of medication, diet and juice when examining patients with supra therapeutic INR levels. This study will warn physicians about the possible interaction between pomegranate juice and warfarin, and suggests that patients should be aware of that warfarin patients be aware of the potential interactions. Patients should be advised to limit and reduce the intake of pomegranate juices, especially who experienced INR fluctuations and any sign and symptoms of warfarin toxicity.

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Conflict of interest

None

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