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Elevated international normalized ratio with the consumption of grapefruit and use of warfarin

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Abstract

A 65-year-old male with documented atrial flutter who was taking warfarin chronically returned to the anticoagulation clinic for follow-up, after having been on 10 mg daily for approximately 2 weeks. He had a previous sub-therapeutic international normalized ratio of 1.7 on a dose of 65 mg/week. The international normalized ratio at this visit was now 4.77 via venipuncture, after just an 8% increase in weekly dosing. He self-reported adherence to the new warfarin dosing but had begun eating grapefruit since last visit. The patient had no active bleeding and was told to decrease his dose to 8 mg daily. He also stopped eating the grapefruit. One week later, he returned to the clinic and the international normalized ratio was 2.1. He is currently back on warfarin 65 mg/week, and his international normalized ratio has been within therapeutic range for the past 4 months. Clinicians should have a heightened awareness of the potential for elevated international normalized ratio when grapefruit juice is consumed in a patient who is taking warfarin.

Keywords

Warfarin, grapefruit, elevation, enzymes, international normalized ratio

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Introduction

Warfarin is the most commonly prescribed anticoagulant in the United States, due to its well-established efficacy in preventing clot formation in high-risk individuals and reducing the risk of cardioembolic stroke.[1] The management of warfarin poses a challenge to many clinicians due to the numerous drug–drug, drug–disease and drug–food interactions.[2] With regard to drug–food interactions, the vitamin K content of foods needs to be taken into account, and in our patient's case, the consumption of grapefruit was of particular concern. There is limited information currently published in the literature on this drug–food interaction.

Case

A 65-year-old male with documented paroxysmal atrial flutter for 10 years has been followed in our anticoagulation clinic for approximately 7 years. In addition to atrial flutter, he has documented systolic congestive heart failure (ejection fraction 30%–40%), hyperlipidemia (controlled), hypertension (not controlled) and a history of alcoholism. He no longer drinks alcohol. He was a former cigarette smoker and quit in 2006.

The patient was seen in our pharmacist-run anticoagulation clinic in October 2012 with a sub-therapeutic international normalized ratio (INR) level of 1.7 (goal INR: 2–3). His warfarin dose was then increased from 5 mg on Fridays and 10 mg from Saturday to Thursday (65 mg/week) to 10 mg daily (70 mg/week); an approximately 8% weekly dose increase. Two weeks later, his INR was 4.77 via venipuncture. The patient reported adherence with his medication and confirmed the dosing of 10 mg each day since his last appointment. The only change was the introduction of grapefruit in his diet (one whole grapefruit each day for 3 days during the week prior to the INR draw). The resulting INR from the lab was 4.77, and his warfarin dose was decreased to 8 mg daily. The patient self-reported adherence with his current warfarin regimen and stated no dietary changes, no bleeding/bruising or changes in medications at that time. The patient's ejection fraction, serum

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creatinine and weight were steady, and there were no signs of a heart failure exacerbation. He was instructed to continue to monitor for signs and symptoms of bleeding or thromboembolism and to report to the emergency room if symptoms arose. He was also instructed to stop eating the grapefruit. It should be noted that the patient had been in therapeutic range 83% of the time for the 6 months prior to this incident.

Five days later, the patient returned to clinic and his INR was 2.1. His basic metabolic panel and liver function tests were normal. Hemoglobin and hematocrit have been chronically slightly low: 13.3 g/dL and 42.2% in November 2012. There were no changes with his other medications. At his next follow-up appointment, it was noted that the patient was back on warfarin, at a dose of 5 mg on Friday and 10 mg from Saturday to Thursday and has been within therapeutic range for the past 4 months.

Discussion

Grapefruit can affect the metabolism of a variety of medications through the cytochrome P-450 enzyme system located in the small intestine and liver. The enzymes that are affected are 3A4, 1A2 and 2A6.[2,3] The (R) enantiomer of warfarin is metabolized by CYP1A2 and CYP3A4, which could contribute to this theoretical interaction of warfarin with grapefruit.[2,3] Two compounds have been cited as potential targets. Naringin is the predominant flavonoid found in grapefruit and is not found in significant amounts among other citrus fruits.[4] The metabolite of naringin, naringenin, has demonstrated significant inhibition of dihydropyridine metabolism in vitro.[5] Dihydroxybergamottin (DHB), which is also in grapefruit, has also been studied, and the most current theory is that a variety of compounds specific to grapefruit may be working together to cause the interactions.[6] Both naringenin and DHB inhibit CYP3A4. Studies have shown a reduction in CYP3A4 content within the small intestines after consumption of grapefruit/grapefruit juice.[7,8] The amount of grapefruit consumed has been found to be related to the extent of the inhibition. Recovery of the lumen CYP3A4 may take up to 3 days after a single serving of grapefruit or grapefruit juice, which is consistent with the time needed for enzyme regeneration.[9] Multiple factors determine the significance of these interactions, including the dose and amount consumed, varying levels of intestinal CYP3A4 and lack of a standard grapefruit juice concentration used in the documented literature. In addition, individual variances in CYP3A4 expression within the small intestine can occur.[3] Based upon a review of the literature, there are no clear differences in the interaction with grapefruit juice versus the actual fruit itself, although the clinical significance is difficult to interpret.

There have been limited clinical studies published which have investigated the possible interaction with grapefruit juice and warfarin.[10–12] In one small controlled trial, 10 men stabilized on warfarin ingested three 8-ounce glasses of grapefruit juice per day for 1 week. There was no significant change in prothrombin time or INR values, and the authors concluded that grapefruit juice did not affect warfarin metabolism.[10] In another small study, grapefruit seed extract (GSE) was given for 3 days to two patients on lifelong warfarin.[11] One patient subsequently developed a minor subcutaneous hematoma 3 days later and her INR was 7.9. In a case report, grapefruit juice was found to be a potential factor in a supratherapeutic INR.[12] A 64-year-old male with atrial fibrillation who was taking warfarin was found to have an INR of 6.29 with no significant bleeding or bruising. The patient admitted that 10 days prior to the appointment, he had begun consuming 1.5 L of grapefruit juice per day. Upon discontinuation of the grapefruit juice, the INR normalized.

With regard to our patient, he had recently started eating grapefruit in the week leading up to his appointment when the INR of 4.77 was detected. Although his warfarin dose had been increased slightly on the previous visit, the weekly increase was only 8% and one wouldn't expect the INR to increase that dramatically (1.7–4.77). After this acute increase in his INR, the patient discontinued consuming any form of grapefruit and his warfarin dose was decreased. Upon his follow-up appointment, his INR returned to a more appropriate level of 2.1. Although his warfarin dose was reduced by 20% in order to decrease the INR acutely, it is clear to us that the cessation of eating grapefruit also was a factor. He is now taking his previous dose (65 mg/week), and the INR has remained in therapeutic range for the past 4 months.

Use of the Naranjo[13] probability scale indicated a possible relationship between the elevated INR and the ingestion of grapefruit in our patient (score of 4). The only negative score on the probability scale related to the fact that alternative causes that could have caused the elevated INR could not be definitively excluded. The information presented in this case does add to the current literature as it relates to drug–food interactions with warfarin and could aid clinicians when performing patient counseling of the medication.

Conclusion

The pharmacokinetic profile and effect of grapefruit/grapefruit juice on CYP3A4 makes an interaction with warfarin definitely plausible, even though the true clinical effect is often debated. Different products and amounts of grapefruit juice/extract are used in the studies and individual variances in CYP3A4 expression within the small intestine is another factor to consider. While it is impossible to say with certainty that consumption of grapefruit was the definitive cause of the elevated INR in our patient, it may be prudent to consider close follow-up and monitoring in patients on warfarin who do wish to eat grapefruit or drink grapefruit juice. Clinicians should instruct patients to avoid grapefruit altogether if elevations in the INR are seen. Appropriate controlled studies

are necessary to fully determine whether a causal relationship exists.

Declaration of conflicting interests

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