REVIEW

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Cranberry Juice and Warfarin: When Bad Publicity Trumps Science

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ABSTRACT

Based on anecdotal reports, the question of whether cranberry juice interacts with warfarin has been raised. This article discusses the potential mechanism, and systematically reviews case reports as well as clinical trials examining the possible interaction. We systematically searched MEDLINE via PubMed, and the Cochrane Library database. Fifteen case reports were summarized, including the initial unpublished brief reports to the Committee on Safety of Medicines and the subsequent 6 published case reports. Seven clinical trials were analyzed, including 3 studies using warfarin and 4 surrogate drugs. Only 2 cases had a validation scale suggesting a "probable" interaction, but even in these patients there were many reasons to question the validity of a relevant drug interaction. Randomized clinical trials and surrogate markers found no evidence to support the interaction between cranberry juice and warfarin. Because the moderate consumption of cranberry juice does not affect anticoagulation, we encourage the reexamination of initial warnings based on scientific evidence. We conclude that the initial precautionary warnings by administrating bodies are limited to anecdotal case reports and represent misleading conclusions.

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KEYWORDS: Anticoagulant therapy; Anticoagulation; Cranberry juice; Drug interactions; Warfarin

The pharmacokinetic and pharmacodynamic behaviors of warfarin are known to be influenced by many factors, including the vitamin K content of diet, liver function, and medications. Many drug-drug interactions influence warfarin pharmacokinetics by their interaction with the P450 metabolic enzymes. Recently, anecdotal evidence has implicated an interaction between cranberry juice and warfarin. Because of several unpublished brief reports of an interaction, in September 2003, the Committee on Safety of Medicines in the UK alerted clinicians to a potential interaction between warfarin and cranberry juice based on 5 cases (including a fatality).[1] By October 2004, the Committee on Safety of Medicines had received 12 unpublished case reports of suspected interactions and advised against concurrent use unless health benefits outweighed risks.[2] Since then, several case reports have been published. In 2005, the US Food and Drug Administration mandated a precautionary potential interaction label on warfarin. The result of the first clinical study examining the interaction became available in December 2006. Despite more objective clinical evidence showing no interaction, in 2008 the Joint Commission began reviewing the safety of cranberry juice in hospitals and advising patients taking warfarin to avoid cranberry juice. Rather than meeting the safety requirements by the Joint Commission, many hospitals have eliminated cranberry juice from their pantries. This chain of events is based on anecdotal cases and does not demonstrate a causal effect linking cranberry juice ingestion and altered international normalized ratio. This article reviews case reports and available clinical trials examining the possible interaction.

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Authorship: Jennifer Zikria performed a literature search, created tables, performed data interpretation for case reports and clinical trials, and wrote the manuscript. Raimonda Goldman performed data interpretation for case reports and reviewed the manuscript. Jack Ansell reviewed, modified, and edited the manuscript.

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MECHANISM

Several mechanisms might explain the potential interaction between warfarin and cranberry juice. The flavonoids in cranberry juice are suspected to inhibit CYP2C9, the enzyme responsible for metabolism of S-warfarin that would increase warfarin levels.[3,4] S-warfarin is the more active enantiomer, whereas R-warfarin is mainly metabolized by CYP3A4 and CYP1A2. Alternatively, cranberry juice flavonoids might displace warfarin from albumin binding sites and transiently potentiate an anticoagulant response.[5]

CLINICAL SIGNIFICANCE

- Cranberry juice has been implicated in interacting with warfarin.
- The alleged interaction between cranberry juice and warfarin is limited to anecdotal case reports that represent harmful and misleading conclusions.
- Randomized clinical trials have found that the moderate consumption of cranberry juice does not affect warfarin anticoagulation.
- Consistency of diet is the cornerstone of dietary advice for treatment of patients taking warfarin.

METHODS

Search Strategy

We did a systematic review of the available literature by searching Medline via PubMed (1950 through April 2009), and the Cochrane Library Database (Cochrane Central Register of Controlled Trials) with MeSH terms and search text words including "cranberry" and "warfarin." There was no date or type of article restrictions.

RESULTS

Anecdotal Case Reports

Several case reports have implicated cranberry juice in international normalized ratio instability. These cases do not prove that instability of anticoagulation was caused by cranberry juice. Most patients had reasonable causes for international normalized ratio instability (dietary changes, serious illness, or concomitant medications). Many patients also drank excessive amounts of cranberry juice that far exceeded moderate consumption. In some cases, the use of warfarin and cranberry juice increased international normalized ratio levels, but in others, the levels decreased. Table 1 summarizes the unpublished brief reports to the Committee on Safety of Medicines[2] in the UK that initially implicated an interaction between cranberry juice and warfarin. Table 2 summarizes the few published individual case reports.[6-11]

Clinical Trials

Formal drug interaction studies have not supported the findings of anecdotal case reports. Objective randomized, double-blind trials have sought to determine whether cranberry juice has an interaction with warfarin. To date, 7 randomized clinical studies have examined whether cranberry juice affects either warfarin or surrogate drugs that are metabolized by the same isoenzymes as warfarin. Table 3 summarizes the clinical trials[12-14] and Table 4 the surrogate studies evaluating the possible effects of cranberry juice.[15-18] See the Figure for a diagram of randomized control trials.

Clinical Trials in Patients with Stable Anticoagulation. Randomized controlled studies present the strongest level of evidence examining the possibility of a cranberry juice interference with warfarin. Li et al[12] performed a randomized, placebo-control, double-blind crossover study in 7 patients who had received a stable dose of warfarin for the past 3 months. Patients were randomized to consume 250 mL (8 oz) of cranberry juice (Cranberry Institute, East Wareham, Mass) or placebo for 7 days, followed by a washout period of 7 days, and then crossed over to the opposite therapy for 7 days. A final international normalized ratio measurement was obtained 3 days after completing the therapy (day 24). The study measured and found no significant change in international normalized ratio from baseline during the 7 days of cranberry juice consumption. Li et al[12] were criticized, however, for their small sample size.

Ansell et al[13] examined the effects of cranberry juice in patients on long-term therapy. In a randomized, double-blind study, 30 patients with stable international normalized ratio measurements for 8 weeks before the study were randomized to drink 8 oz of cranberry juice (Ocean Spray, Lakeville-Middleboro, Mass) or placebo. There was a 2-week lead-in phase with weekly international normalized ratio measurements, followed by a 2-week intervention phase when subjects consumed either cranberry juice or placebo, with measurements of international normalized ratio and warfarin isomer levels every 3 days. This was followed by a 1-week follow-up international normalized ratio to exclude a delayed effect. Like Li et al,[12] Ansell's study found no significant change in warfarin with concomitant administration of cranberry juice.[13] Plasma warfarin enantiomer levels and peak warfarin levels were unchanged when drinking cranberry juice. The study concluded that drinking 8 oz of cranberry juice daily had no effect on the international normalized ratio in patients on warfarin therapy, but the investigators could not exclude the effects of larger amounts of cranberry juice.

Clinical Trials in Healthy Volunteers. Abdul et al[14] performed an open-label, 3-treatment, randomized crossover study with 12 healthy males with known CYP2C9 and VKORC1 (vitamin K epoxide reductase subunit 1) geno-