

Cranberry Juice and Warfarin: What More Have We Learned?

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In 2006, this column reviewed the available literature on the potential for an interaction to occur between cranberry juice and warfarin.¹ At that time, there were several case reports of patients who appeared to have experienced increased international normalized ratio (INR) values following the consumption of cranberry juice. One study had also been published that examined the potential for cranberry juice to affect the metabolic activity of the enzyme cytochrome P450 2C9 (CYP2C9), which is considered to be the most important in determining warfarin metabolism.

This study failed to find an effect of a single 8-oz dose of cranberry juice on the metabolism of the CYP2C9 substrate flurbiprofen (Ansaid).² As data were quite limited in 2006, we suggested that avoiding cranberry juice while taking warfarin was a “very conservative” but rather harmless approach to the potential interaction. Because additional case reports as well as several controlled clinical trials have been published since then, it would seem useful to revisit this interaction.

CASE REPORTS

Case reports of INR changes have appeared in the literature and have been reported to government drug safety committees.³⁻⁶ As is often typical with case reports of warfarin interactions, many of the patients had confounding variables (eg, infection, use of other drugs, diet changes other than cranberry juice, degree of adherence, polymorphisms for CYP2C9 and vitamin K

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epoxide reductase [VKORC1]) that could account for the observed INR changes. Some noted decreased INR with cranberry juice, and one reported an increased INR with cranberry juice in the absence of warfarin administration. In addition, the amount of cranberry juice consumed was not noted in several of the case reports, while others reported consumption of cranberry sauce or very large amounts of cranberry juice. The importance of these external factors should not be underestimated, as a recent study was able to account for only about 50% of the variability in warfarin dosing by accounting for genetic polymorphisms controlling warfarin metabolism and VKORC1, body surface area, and patient age.⁷

PROSPECTIVE STUDIES

In a study of 30 patients stabilized on warfarin who were randomized to placebo or 8 oz of cranberry juice daily for 2 weeks, no change was noted in the plasma concentration of warfarin nor in the patients' INRs.⁸ In another study done in patients taking warfarin, subjects received 250 mL of cranberry juice or placebo for 7 days in a randomized, crossover design.⁹ Warfarin plasma concentrations were not measured; however, no changes were observed in INRs when cranberry juice was administered, compared with placebo. Twelve healthy subjects each received a single, 25-mg dose of warfarin, alone or after 2 weeks of concentrated cranberry extract tablets, 1000 mg 3 times daily.¹⁰ It

is unknown how cranberry concentrate relates to cranberry juice, but the dose is higher than recommended (600-800 mg of extract daily) for urinary tract effects. No change in warfarin plasma concentration, protein binding, platelet aggregation, or the activity of clotting factors II, VII, or X was noted. The authors reported a modest (28%) increase in the mean area under the curve of INR (increased INR seen in 6 of 12 subjects) during cranberry treatment. They declared this to be significant (no *P* value reported) using a 90% confidence interval, instead of the usual 95% value. The clinical significance of this change is unknown but appears to be limited.

SUMMARY

The interaction between cranberry juice and warfarin seems to be following the pattern set by other purported interactions with warfarin. Several cases are reported where a temporal relationship appears to exist between the suspected precipitant drug and a change in patient response to warfarin. The cases often lack sufficient detail or include confounders that make it impossible to establish causation. When prospective, controlled studies are done, the interaction is not observed. This is similar to the situation with warfarin and some antibiotic interactions.

A patient's response to warfarin depends on many variables, some of which we do not understand. This makes it more likely that events associated with warfarin use might be invoked as responsible for unexpected changes in response. Not only is a temporal relationship necessary to establish causation, but a plausible mechanism must also be described.¹¹ It would appear that, like most grapefruit juice interactions, the consumption of usual amounts of cranberry juice presents minimal risk to patients taking warfarin. **PT**

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