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Warfarin and Cranberry Juice: Time to Lose the Warnings?

Expert Interview With Jack E. Ansell, MD

Linda Brookes, MSc

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A Best Evidence Interview With Jack E. Ansell, MD

The Best Evidence Study

Dr. Ansell is senior author of the following review:
Zikria J, Goldman R, Ansell J. Cranberry juice and warfarin: when bad publicity trumps science. *Am J Med*. 2010;123:384-392.

This study was selected as the subject of this interview because of its high ranking in Medscape Best Evidence, which uses the McMaster Online Rating of Evidence System. Of a possible score of 7, clinicians who used this system ranked this study as 6 for relevance and 5 for newsworthiness

About the Interviewee: Jack E. Ansell, MD

Jack E. Ansell, MD, is the Chairman of the Department of Medicine at Lenox Hill Hospital and Professor of Medicine, New York University School of Medicine, New York, NY. Dr. Ansell's main areas of research focus on the clinical problems of thrombosis, thrombotic disorders, and antithrombotic therapy. He has had a continued involvement in the application of new modes of delivering and monitoring anticoagulants, particularly

in the management of oral anticoagulant therapy. He has been increasingly involved in the clinical study of new oral anticoagulants.

Dr. Ansell is the founder and immediate past Chair of the Anticoagulation Forum, a network of anticoagulation clinics throughout North America, and is a member of professional organizations, including the American College of Physicians (Fellow), the American Society of Hematology, the International Society of Thrombosis and Hemostasis, the American Heart Association (Fellow), and the American Medical Association. He is Chair of 2 consensus committees of the American College of Chest Physicians that are working to establish national guidelines on antithrombotic therapy.

Dr. Ansell is the author of more than 200 publications, including original research, reviews, editorials, chapters, and books. He serves as Senior Associate Editor for the *Journal of Thrombosis and Thrombolysis* and as an editorial consultant for professional journals, including *The New England Journal of Medicine*, *Blood*, *Journal of Thrombosis and Haemostasis*, and *Circulation*.

Background to the Interview

In the United States, current prescribing information for warfarin (Coumadin®) lists cranberry (*Vaccinium macrocarpon*) products as one of the botanical (herbal) medicines associated with an increase in the effects of the anticoagulant warfarin.[1] Patients receiving warfarin are advised to avoid intake of cranberry juice or any other cranberry products. This warning of a potential interaction was originally approved by the US Food and Drug Administration (FDA) in 2006.[2] It followed an advisory issued by the UK Medicines and Healthcare Products Regulatory Agency (MHRA)/Committee on Safety of Medicines (CSM) in 2004 stating that patients taking warfarin should avoid cranberry products unless the health benefits clearly outweigh the risks and that product information for warfarin should be updated to reflect this advice.[3,4] This advice was based on 12 poorly documented reports of suspected interactions involving warfarin and cranberry juice, 8 involving increases in international normalized ratio (INR) and/or bleeding episodes, 3 cases in which INR was unstable, and 1 case in which the INR decreased. An earlier warning to limit or avoid cranberry consumption concurrent with warfarin use had been issued by the MHRA/CSM in 2003 after the first 5 reports of interactions were received.[5] Since none of the reports defined a safe quantity or brand of cranberry juice or noted any difference between cranberry juice and other cranberry products with concurrent warfarin, similar caution was advised with all cranberry products. In Canada, Health Canada announced in 2004 that following the UK advisory, it would continue to monitor this and other potential warfarin interactions,[6] and in 2005, it placed cranberry juice on a list of food products that "may affect warfarin levels" as opposed to products for which evidence suggested that they "may change levels of warfarin in the bloodstream or may directly affect blood clotting on their own."[7] None of these warnings about the potential warfarin-cranberry interaction has been modified since the warnings were first issued.

Few studies have been carried out to determine a possible mechanism for this potential interaction. Because warfarin is a racemic mixture of the *R*- and *S*-enantiomers, with the *S*-enantiomer having 2-5 times more anticoagulant activity than the *R*-enantiomer, it was proposed that certain flavonoids in cranberry juice or cranberry products might inhibit cytochrome P450 (CYP) 2C9, the enzyme responsible for the hepatic elimination of *S*-warfarin. Study results have been consistent, showing no effect on CYP2C9, although some questionable effect on the less important enzyme, CYP3A4.[8-13]

One of the 3 randomized clinical trials that investigated the effects of cranberry juice on warfarin-stabilized patients was carried out by Dr. Ansell and colleagues at Boston University School of Medicine.[10] The study, which was supported by Ocean Spray Co. (Lakeville-Middleboro, Massachusetts), manufacturer of the juice used, and the US Department of Health and Human Services, found that in 30 patients receiving long-term warfarin, 2 weeks' consumption of cranberry (240 mL once daily) had no effect on plasma *S*- or *R*-warfarin plasma levels compared with placebo. Mean INR did not differ significantly between the 2 cranberry and placebo groups except at one time point (day 12; $P < .02$) but then returned to previous levels, which the investigators suggested was unlikely to be clinically important and might be a random change. This and other clinical evidence was reviewed by Dr. Ansell and colleagues at Lenox Hill Hospital in their recent paper.[14] They examined 6 published case reports and 7 clinical trials (3 that used warfarin and 4 surrogate drugs) identified

from MEDLINE via PubMed and the Cochrane Library database, along with 9 unpublished case reports originally submitted to the UK CSM.[4] The authors concluded that given the "poor quality of the case reports and the almost uniform findings in randomized studies," the FDA and CSM advisories should be reconsidered. Like 2 previous reviews,[15,16] Dr. Ansell and co-authors concluded that that there is no evidence of a clinically relevant interaction when cranberry juice is consumed in moderation, although they did not rule out that consuming large quantities of cranberry juice might affect warfarin.

Dr. Ansell spoke with Linda Brookes, MSc, for Medscape, to discuss the evidence for and against a warfarin-cranberry juice interaction, as recently reviewed, and the way in which regulatory bodies assess data from clinical reports and studies before warnings are issued about potential interactions with drugs, such as warfarin.

The Interview

Medscape: Was the aim of your review to present evidence to support a call for removal of the regulatory warning about a warfarin-cranberry juice interaction (increased bleeding) or to highlight the poor quality of the adverse reaction reports on which this warning was based?

Dr. Ansell: I think we aimed to address both of these points. The warning that there is a potential to enhance the effect of warfarin (prolonging the INR) with cranberry juice intake is absolutely not true. That perception is based on what I believe are faulty reports, many of which are not even case reports, but case comments consisting of a few sentences about a possible interaction. This goes back about half a dozen years, when there were a number of case reports sent to the regulatory authority in Great Britain.[3,4] Again, I hesitate to call them "case reports," because they were really just reports that said, "I had a patient who was drinking cranberry juice, and her INR went up, and I stopped it, and the INR came back, and there must be an interaction." If you read these reports, you see that they merely describe a variety of different problems, often in very sick patients with multiple factors that could influence the INR. They are not detailed in any way, nothing more than a few sentences. In some cases, patients were drinking several liters of cranberry juice a day to the exclusion of other foods[17]; some patients were extremely ill[3,18]; and in one case, the INR actually went down as opposed to going up like in the other reports,[3] but that was still taken into consideration. How can you even incriminate a drug interaction where in one case, the INR goes up, and in one case, it goes down? It does not make scientific sense. There were multiple other potential interactions, and as a consequence of these reports, the British authorities issued an advisory that patients receiving warfarin should avoid or be careful with cranberry juice.[4,5] Then there were 1 or 2 more formal case reports in the medical literature,[19,20] again of doubtful validity, as many case reports are, and as a result, the FDA issued an advisory to Bristol-Myers Squibb Company, which manufactures Coumadin, to change the package insert and issue a warning. Around the same time, there were 1 or 2 small randomized controlled trials, the results of which suggested that, in fact, there was not an interaction.[8,9] These were well-done studies, certainly all much better than an anecdotal case report, and that stimulated me to do a study, published in 2009, that was a randomized, double-blind trial comparing intake of cranberry juice with placebo in 30 patients on stable warfarin anticoagulation (INR, 1.7-3.3). Again, it showed no interaction.[10] As far as drug interaction studies go, this was a reasonably sized drug interaction trial. It was fairly robust in its design, and the patients drank what would be considered an average amount of cranberry juice (240 mL daily). This study was clearly a negative study. So based on the anecdotal reports, my study, and some other randomized trials and surrogate trials that are outlined in the review, we published the story to say that, in fact, it is really not true that there is an interaction and that there should be no problem with patients drinking cranberry juice and warfarin, if they so desire. I certainly cannot say that overwhelming consumption of cranberry juice might not have some interaction. We did not study that possibility, and some of the anecdotal reports involved people who drank liters of cranberry juice daily,[17,19] but I think for the average or moderate consumption of cranberry juice, there is no concern. I think this whole thing has gotten out of hand to the degree that hospitals are avoiding cranberry juice in their nutritional repertoire, which just does not make sense.

Medscape: The MHRA has said that it is continuing to receive reports of adverse reactions, and the FDA does not appear to have changed the warning since it was issued. What do you think the regulatory authorities should be doing about this?

Dr. Ansell: My suggestion is that the FDA and the MHRA should look at the peer-reviewed evidence and make decisions based on good, evidence-based medicine, which I would like to think that they do. Unfortunately, this is not the case, and I believe this is a classic example where bad science has influenced public decision-making. If you look at some of the reviews of drug interactions in general, and particularly with warfarin, such as the review by Holbrook and colleagues published about 5 years ago in the *Archives of Internal Medicine*,[21] which was a good comprehensive review and update of a previous article that they wrote,[22] the overwhelming majority of drug interaction reports were anecdotal. The overwhelming majority were of such poor quality that actual interactions were unlikely. So the situation with the assumed cranberry-warfarin interaction is just another example of that happening.

Medscape: Recently, John R. Horn, PharmD, and Philip D. Hansten, PharmD (University of Washington School of Pharmacy, Seattle, Washington), said that the history of the cranberry juice-warfarin interaction seemed to be following a pattern set by other purported interactions with warfarin, including some with antibiotics.[23] They observed that, "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."

Dr. Ansell: I believe that is exactly how this happened.

Medscape: Has there been any more data about the pharmacokinetics and pharmacodynamics of cranberry juice lately? There was a paper published recently in the *Journal of Experimental Pharmacology*,[12] in which a cranberry juice brand that inhibited CYP2C9 in isolated liver microsomes failed to do so in healthy participants given a single 10-mg dose of warfarin. What might be the reason for that? Would it be because of some transformation that occurs in vivo that does not occur in vitro?

Dr. Ansell: I do not know, but up to the present time, there has been no significant explanation of how cranberry juice might interact with warfarin, and in fact, the evidence suggests that it does not interact with warfarin.

Medscape: Cranberry juice is drunk for health effects, not just because people like the taste, so it is really an unregulated supplement, with little evidence for some of the health claims made for it. Warfarin is considered a difficult-to-manage drug by most physicians. Aren't the regulatory authorities just being extra cautious about a possible interaction?

Dr. Ansell: I think they are being ultracautious in recommending avoidance just because of the outside possibility of an interaction, but I do not believe that is the way we should practice medicine or advise the public.

Medscape: But cranberry juice is not a medicine and has not gone through any regulatory approval process.

Dr. Ansell: The regulatory agencies should have based their decisions on firm evidence, and I think the evidence for an interaction with cranberry juice is really nonexistent in terms of good controlled trials and the anecdotal reports are just not trustworthy.

Medscape: Despite all the good-quality evidence to the contrary, it still seems to be the generally accepted opinion that cranberry juice is dangerous for patients receiving warfarin. There was a paper presented at the Heart Rhythm Society meeting in Denver in June about a "communication gap" in educating patients about warfarin. The abstract said that "bleeding events have been linked to the use of ... cranberry," among other "supplements.[24]" This was widely quoted in the media reports.[25,26]

Dr. Ansell: I agree with you, it still is the accepted view, and I hear it all the time from practitioners who send me emails.

Medscape: So practitioners still do believe this?

Dr. Ansell: Yes. The wrong message gets out very quickly; the right message is just difficult to get out.

Medscape: Who do you think should be responsible for getting the right message out?

Dr. Ansell: I cannot say that anybody should be responsible. The people who have a vested interested in reversing this are obviously the cranberry producers. My interest is to try to present the science in a correct fashion and to inform the public, but to change public perception of something that has been created by the FDA and other advisory bodies is very difficult.

Medscape: Presumably physicians who are communicating with patients taking warfarin want to be very clear about what their patients can and cannot do, because there is a long list of potential interactions.

Dr. Ansell: Many physicians, I believe, advise patients incorrectly about dietary prohibitions. Patients should be able to eat what they want to eat, and they should not have to change their diet on warfarin. The message they should get is that they need to have a consistent diet from week to week, meaning that they should not go on diet binges or change dramatically for any period of time. Physicians should adjust the warfarin dose to accommodate their diet. One problem with warfarin therapy is that it leads to problems with quality of life because of all the dos and don'ts, and this affects adherence and patients' desire to take warfarin. Warfarin has a long history and tradition, and it is hard to change what physicians have traditionally done.

Medscape: For years, patients and physicians have been anticipating alternatives to warfarin that will be easier to use. Some have come close but failed in late development. Now there are new drugs on the horizon, such as the direct thrombin inhibitor dabigatran and the factor Xa antagonists apixaban and rivaroxaban. Is it likely that any of these will be used widely in the future to replace warfarin and make patients' lives easier so that they will not have to worry about whether they drink cranberry juice or not?

Dr. Ansell: Yes, undoubtedly the future holds the potential for new anticoagulants, such as rivaroxaban, apixaban, or dabigatran, which are the 3 drugs furthest along in development. These drugs have few, if any, drug interactions and no significant dietary interactions, and their anticoagulant affect is predictable, so they do not, in a general sense, require routine monitoring. As a substitute or an alternative to warfarin, these drugs will make life much each easier for the physician, as well as for the patient. On the other hand, they will not replace warfarin entirely; not everybody is immediately going to switch to one of these new agents. Assuming that these drugs will be successful and approved over the next couple of years, however, I think they will have a major effect on the population of patients taking warfarin. But warfarin will not go away; there will be many patients still taking that drug.

Medscape: But maybe for the majority, the dietary interactions, even the one with cranberry juice that probably doesn't exist anyway, will no longer be a concern.

Dr. Ansell: I agree. I think that patients will be major advocates for switching to these new drugs, because many of them do not like to take warfarin because of the complexity and the difficulty of use and the quality-of-life issues.

Summary Points

The warning that there is a potential to enhance the effect of warfarin prolonging the INR with cranberry juice intake is mostly based on faulty reports, many of which are not even case reports but case comments consisting of a few sentences about a possible interaction. On the basis of anecdotal reports, the current study, and other randomized and surrogate trials, there should be no problem with patients taking warfarin drinking average or moderate amounts of cranberry juice.

The history of the cranberry juice-warfarin interaction seems to follow a pattern set by other purported interactions with warfarin, including some with antibiotics, in which 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.

Physicians should advise patients to have a consistent diet from week to week and not go on diet binges or change their diet dramatically for any period of time. The physicians can then adjust the warfarin dose to accommodate their diet.

New anticoagulants, such as rivaroxaban, apixaban, or dabigatran, appear to have few, if any, drug interactions and no significant dietary interactions, and their anticoagulant effect is predictable, so they do not, in a general sense, require routine monitoring. As a substitute or an alternative to warfarin, these drugs will make life much each easier for the physician, as well as for the patient. On the other hand, they will not replace warfarin entirely; not everybody is immediately going to switch to one of these new agents.

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