

ANTICOAGULATION FORUM

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Cranberry Juice & Warfarin: Is There an Interaction?

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A great deal of recent attention has been focused on possible interactions of prescription drugs with foods, nutrients, and natural medicines. One important example is the possible effect of grapefruit juice on the plasma levels of certain prescription medications. Natural substances in grapefruit juice—principally furanocoumarin derivatives—have the capacity to inhibit Cytochrome P450 3A (CYP3A) enzymes present in the wall of the gastrointestinal tract. This property of grapefruit juice accounts for a number of clinically important drug interactions, in which administration of grapefruit juice along with or prior to certain medications causes higher plasma levels and greater effects of these medications¹⁻⁶.

In contrast to grapefruit juice, the occurrence of drug interactions with other common beverages is not well established. In several anecdotal reports from the United Kingdom (UK), administration of cranberry juice has been associated with an enhanced antithrombotic effect of the anticoagulant warfarin^{7, 8}. It has been speculated that

some natural component of cranberry juice could inhibit the activity of Cytochrome P450-2C9 (CYP2C9), the enzyme responsible for metabolism of S-warfarin⁹⁻¹¹ (which is the “enantiomer” of warfarin responsible for its anticoagulant effect). This would lead to higher S-warfarin plasma levels, and thereby increased anticoagulant activity. Even though there is no credible scientific evidence to support this explanation¹¹, the UK Committee on Safety of Medicines (CSM) issued the following warning: “Patients taking warfarin should avoid taking cranberry juice or other cranberry products unless the health benefits are considered to outweigh risks”¹². The report states that the CSM received a total of 12 reports of suspected interactions involving warfarin and cranberry juice. The CSM concludes that “there is now sufficient evidence of an interaction for formal advice to be issued.”

These reports, and the regulatory action that resulted from them, have naturally caused many warfarin-treated patients to worry that consumption of cranberry juice might cause their anticoagulant regulation to go out of control, and therefore could be a health risk.

Our research group at Tufts University School of Medicine and Tufts-New England Medical Center has long been concerned with realistic hazards of drug-nutrient interactions. The questions we ask include: What are the sources of accurate, valid information about drug-nutrient interactions? Which interactions pose a realistic health concern, and which constitute no real health hazard? How is information on this topic best distributed to the public? What research studies need to be conducted to address concerns about

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NCBAP Update

The NCBAP board has had numerous meetings to work on updating the CACP application process as well as creating an on-line exam for recertification. Please visit www.ncbap.org for updates on the progress of the on-line exam and for the location and date of exams in 2006.

The CACP exam was administered in December 2005 at the American Society of Health-System Pharmacists (ASHP) Mid-Year Clinical Meeting in Las Vegas, NV.

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Save the Date! May 3-5, 2007

Planning is underway for the Anticoagulation Forum's next biannual meeting. The 9th National Conference on Anticoagulant Therapy will be held May 3-5, 2007 in Chicago, Illinois at the Marriott Chicago Downtown hotel. Conference programs will be mailed in late fall. Please mark your calendars and plan on attending this important meeting. We look forward to seeing you there!

Congratulations to the following individuals who successfully met all of the application requirements and passed the certification exam:

Douglas Anderson, PharmD Albany, GA
Diane Barton, RN APO, AE
Susan Baur, RN Hudson, MA
Vicky Chan, PharmD Baltimore, MD
Peter Fong-Po Cheng, PharmD Monterey Park, CA
Forrest Craig, RPh York, PA
Kristyn Dayton, RN Amesbury, MA
Kathleen Donahue Chelmsford, MA
Molly Englert-Walbrown, PharmD York, PA
Susan Ertel North Oaks, MN
Neha Gada, PharmD Philadelphia, PA
Beverly Gordon, RN Casa Grande, AZ
Teresa Hoffmann, PharmD Lima, OH
Maureen Howard, APRN Freehold, NJ
Brad Joseph, PharmD Bluffton, OH
Catherine Lewis, PharmD Morgantown, WV
Debora Linse, RPh Oklahoma City, OK
Bethany Lowe, PharmD Odenton, MD
Cecilia Mullen, APN Milton, MA
Muna Nour, PharmD, RPh Silver Spring, MD
Amy Peng, PharmD Temple City, CA
Rosa Pham, PharmD Pasadena, CA
Michelle Schymik, PharmD Evansville, IN
Jason Thompson, PharmD Choctan, OK
Karen Wall, PharmD Wallingford, CT
Andrew Wilcox, PharmD Rockton, IL
Jennifer Winters, RPh Canton, OH

The following people were recertified after first taking the exam 5 years ago:

Laura Brown, RPh Austin, MN
Rebecca Cheek, PharmD London, KY
Susan Fugate, PharmD Edmond, OK
Susan Johnson, PharmD East Greenwich, RI
Sharon Kennedy-Norris, PharmD Kitts Hill, OH
Nita Marceau, PharmD Columbia Falls, MT
Sharon Nelson, APN Goleta, CA
Ingrid Stites, APN Louisville, NE

The Certified Anticoagulation Care Provider credential is governed and awarded by the NCBAP and is the only multidisciplinary credentialing opportunity in the United States. This certification process is designed and intended for practitioners whose primary role as an anticoagulation provider includes systematic, organized, and on-going patient education and drug therapy management. ■

Lori Preston, MBA,
Vice President of NATT, lpreston@keelan.com
Elizabeth Varga, MS,
NATT Board Member, varga-5@medctr.osu.edu

NATT's Mission and Goals

The National Alliance for Thrombosis and Thrombophilia is a nation-wide, community based, non-profit volunteer health organization formed in August 2003. In keeping with our goal to ensure that people suffering from thrombosis and thrombophilia receive early diagnosis, optimal treatment and quality support, we have many initiatives underway for 2006.

New Epidemiological Data

New findings presented at the 47th annual meeting of the American Society of Hematology (ASH) showed that each year, hundreds of thousands of Americans die from complications of deep-vein thrombosis (DVT). Findings revealed that more than 600,000 people in the US suffer from symptomatic VTE events each year (DVT, n=376,365; PE, n=237,058). There are almost 300,000 fatal VTE events each year (n=296,370), and only seven percent of those who died were diagnosed and treated. (Heit, J. et al. Blood 2005;106:267a). NATT members are working to increase awareness of these sobering statistics through local media campaigns and NATT's brochures and website.

2006 NATT Initiatives

We organized and planned two patient education seminars. Our first seminar took place on Saturday, March 4th at the University of North Carolina in Chapel Hill. The Chair of our Medical and Scientific Advisory Board, Dr. Stephan Moll, and Board member Pat Koppa both facilitated the free seminar, attended by 130 people, to answer questions regarding blood clots. The second patient education seminar will take place at Ohio State University on May 13, 2006. (Schedule and location will be available on www.nattinfo.org at the beginning of April 2006).

NATT will have its spring newsletter available on-line by mid-March in honor of March DVT Awareness Month. Please read the latest newsletter at www.nattinfo.org/news.htm

Fundraising events held in 2006 have served the dual function of raising awareness of blood clots and blood clotting disorders and generating funds to support NATT's mission. Several more events are planned for the spring and summer.

NATT has been invited by the National Quality Forum (NQF) to participate in a one day summit to discuss consumer messages, research gaps and funding opportunities regarding DVT. The National Quality Forum is a voluntary consensus standard-setting organization.

In May, NATT president Mark Jablonski and NATT Medical and Scientific Advisory Board Chair, Dr. Stephan Moll, will both participate

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Anticoagulation Forum Board of Directors

Jack Ansell, M.D.

It is with great pleasure that I welcome six new members to the Anticoagulation Forum's Board of Directors. Richard Becker, Mark Crowther, Elaine Hylek, Amir Jaffer, Stephan Moll and Edith Nutescu were voted in during the organization's annual meeting, held March 22, 2006 in Chicago, IL. I am extremely pleased to have these new members join me on our board as they bring tremendous skills, talents and experience in the field of anticoagulation. Together we hope to continue growing the Anticoagulation Forum and working to improve the quality of patient care.



Pictured left to right, back row: Alan Jacobson, Stephan Moll, Amir Jaffer, Geno Merli; front row: Richard Becker, Edith Nutescu, Ann Wittkowsky, Jack Ansell, Liz Goldstein, Elaine Hylek, Lynn Oertel. Mark Crowther not pictured.

Anticoagulation Forum 2006 Board of Directors

Jack Ansell, *Boston Medical Center, Boston, MA*
Richard Becker, *Duke University Medical Center, Durham, NC*
Mark Crowther, *St. Joseph's Healthcare, Hamilton, Ontario, Canada*
Elaine Hylek, *Boston Medical Center, Boston, MA*
Alan Jacobson, *Thrombosis Research Group, Loma Linda, CA*
Amir Jaffer, *Cleveland Clinic, Cleveland, OH*
Geno Merli, *Jefferson Antithrombotic Therapy Service, Philadelphia, PA*
Stephan Moll, *University of North Carolina, Chapel Hill, NC*
Edith Nutescu, *University of Illinois, Chicago, IL*
Lynn Oertel, *Massachusetts General Hospital, Boston, MA*
Ann Wittkowsky, *University of Washington Medical Center, Seattle, WA*

Conference Proceedings

The Journal of Thrombosis and Thrombolysis has published the Anticoagulation Forum's 8th National Conference on Anticoagulant Therapy conference proceedings. This issue includes manuscripts by each of the conference speakers as well as all of the abstracts that were presented at the conference. To request a free copy of the journal, please email Liz Goldstein at elizabeth.goldstein@bmc.org with your mailing address.

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Cranberry Juice & Warfarin:

drug-nutrient interactions?

In taking on the question of the possible interaction of cranberry juice and warfarin, we first reviewed in detail each and every case report from the UK that was alleged to demonstrate this interaction. The case summaries were either published in the literature, or were provided by the UK CSM. Based on our review, not a single one of these cases plausibly demonstrated that loss of anticoagulant control was caused by cranberry juice. Some patients had other obvious reasons for loss of control, such as dietary changes, serious illness, or use of other medications. One case even purported to show a lowering effect on the INR by cranberry juice. In a number of cases, insufficient information was available to come to a reasonable judgment of what was happening. None of the cases was properly put in the context of the real challenges of warfarin anticoagulation—many patients experience fluctuating INR levels for no apparent reason, cranberry juice aside. To summarize our own assessment of these case reports—we could not see a reason to implicate cranberry juice as a cause of loss of warfarin anticoagulant control, and we certainly could not understand the reason for the regulatory action taken by the UK CSM.

Next we looked to research models that could help settle this question. The first model involved a “metabolic surrogate”—a medication metabolized in exactly the same way as S-warfarin, that could be safely studied in healthy volunteer subjects. The surrogate is flurbiprofen, a nonsteroidal anti-inflammatory drug which, like S-warfarin, is metabolized by the CYP2C9 enzyme. We administered a single dose of flurbiprofen to a series of healthy volunteers twice: once after two typically-sized drinks of cranberry juice, and on another occasion after two drinks of a “placebo,” having similar color and taste as cranberry juice, but containing no cranberry ingredients. By measuring plasma flurbiprofen concentrations at multiple times after each of the two flurbiprofen doses, we can infer whether cranberry juice affects the activity of CYP2C9. This study has been completed and published¹³. Cranberry juice had no effect on plasma levels of flurbiprofen. This implies no effect on CYP2C9, and also no effect on S-warfarin.

A randomized, double-blind, placebo-controlled trial is now underway, and should be completed within a few months. Patients on warfarin anticoagulation, with stable INR values, are randomly assigned to receive either cranberry juice or placebo for a period of two weeks, during which INR values continue to be followed. This study directly addresses the possibility of interference with warfarin anticoagulation in the real-life setting of anticoagulant treatment.

The story is not yet fully complete, but the available scientific evidence does not support a need for concern about a hazard of cranberry juice consumption by warfarin-treated patients. We will provide further updates as scientific studies are brought to completion.

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NATT Update

in a workshop on Deep Vein Thrombosis. This meeting will take place at the Office of the Surgeon General, National Institutes of Health National Heart, Lung, and Blood Institute.

How NATT can assist AC Forum Members

We have created a new "Treatment of Thrombosis" brochure which defines the two main types of clots and describes the various anticoagulation treatments currently available. Health care providers can access this brochure as well as other NATT patient education materials at www.nattinfo.org/learn-resources.htm. These downloadable PDF files can be used in anticoagulation and thrombosis clinics as handout education materials to patients. Four new brochures, "Postthrombotic Syndrome," "Antithrombin Deficiency," "Vitamin K and Warfarin," and "Antiphospholipid Syndrome" are also nearing completion.

How AC Forum Members can assist NATT

NATT would like to promote greater awareness of thrombosis and thrombophilia among patients. AC Forum health care providers can inform their patients about NATT by downloading NATT patient information at www.nattinfo.org/natt_broch.pdf. This brochure can be printed and given to patients. In addition, AC Forum members can assist in building NATT's resource library. If you have print or electronic patient education resources that you would like to make us aware of, please contact us at nattinfo@yahoo.com ■

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Cranberry Juice & Warfarin:

Disclosure: Dr. Greenblatt has served as a consultant to the Florida Department of Citrus. He also serves as co-investigator on a clinical trial of the interaction between cranberry juice and warfarin supported by a grant from the Cranberry Institute.

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