P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

FILE: ▪Complementary and Alternative Medicine
▪Warfarin
▪Bleeding

HC 100671-340

Date: November 15, 2007

RE: Longitudinal Analysis of CAM Products and Warfarin-related Bleeding

Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. *Pharmacotherapy*. Sep 2007;27(9):1237-1247.

Warfarin is a common anticoagulant drug associated with adverse events connected to diet, concomitant disease, and drug interactions. Dietary supplements and other forms of complementary and alternative (CAM) could theoretically interact with warfarin, resulting in adverse events. It has been difficult to study the potential warfarin interactions of CAM because patient CAM use fluctuates. In addition, patients often do not inform their health care providers of their CAM use, and it is often not documented in patient medical records, further hampering research. The purpose of this prospective longitudinal study was to determine the risk of adverse events, including bleeding episodes and supratherapeutic coagulation, when warfarin was used together with various forms of CAM, including herbal dietary supplements.

Subjects receiving warfarin for a variety of conditions were recruited from St. Paul's Hospital (Vancouver, British Columbia, Canada) between June 1, 2001 and December 31, 2003. For 16 weeks, the subjects recorded information on warfarin use, bleeding events, and the use of 39 CAM therapies in a standardized diary. The subjects also recorded information on other lifestyle factors that could cause bleeding events or supratherapeutic coagulation. The subjects were not told that the focus of the study was CAM-warfarin interactions, in order to avoid recall bias. In addition, the patients' international normalized ratio range (INR) was recorded. Subjects were paid $25.00 (Can) upon return of the diaries.

A total of 171 subjects were enrolled, and 159 completed at least 15 weeks of the study. The INR was measured at least once for 155 subjects. About 46% (n=78) reported using at least one form of CAM during the study period, including 73 subjects who used at least one

CAM product previously associated with warfarin interactions. Among all participants 51% experienced a period of increased bleeding or supratherapeutic INR. Of the 78 subjects using CAM, 47% (n=37) recorded using it throughout the 16-week study period. Vitamin E was the most commonly used CAM therapy (26%). About half of the subjects used drugs known to interact with warfarin, including amiodarone and omeprazol, and two-thirds of the subjects recorded using non-prescription drugs that interact with warfarin, most commonly acetaminophen. A positive, but non-significant association was found between supratherapeutic INR and bleeding episodes. The use of acetaminophen, high target INR, diarrhea, increased alcohol consumption, and advanced age were all associated with a statistically significant increased risk for self-reported bleeding events.

All 39 CAM modalities, except for salmon oil and vitamin E, were associated with at least 1 bleeding episode. In the adjusted model, the following supplements were individually associated with a statistically significant increased bleeding event risk: cayenne pepper (*Capsicum* spp.) (OR 8.0, 95% CI 3.57-17.92), coenzyme Q_{10} (OR 3.91, 95% CI 2.09-7.31), ginger (*Zingiber officinale*) (OR 6.63, 95% CI 3.49-12.61), Saint John's wort (*Hypericum perforatum*) (OR 4.70, 95% CI 1.49-14.79), and willow bark (*Salix* spp.) (OR 9.00, 95% CI 6.42-12.62). The use of 2 or more CAM therapies was also associated with a statistically significant increased bleeding event risk (OR 2.11, 95% CI 1.07-4.16). CAM use was not associated with an increased supratherapeutic INR. After adjusting for other factors that may affect bleeding event risk in the multivariate analysis, only 2 supplements emerged as statically significant independent risk factors for a bleeding event: coenzyme Q_{10} (OR 3.69, 95% CI 1.88-7.24) and ginger (OR 3.20, 95% CI 2.42-4.24).

The authors conclude that this study indicates that ginger and coenzyme Q_{10} may be associated with an increased risk of bleeding events when taken concomitantly with warfarin. The subjects in this study represent a typical cross-section of patients who take warfarin in terms of sex, age, and illness. Therefore, these results can be generalized. Patients taking warfarin should use caution with ginger, coenzyme $Q_{10,}$ and other CAM and non-CAM bleeding event risk factors. This is especially true of high doses and combining suspected risk factors. In addition, improved communication and education about CAM is needed among healthcare providers and patients. More research is required to confirm these results of this prospective study.

A small Australian study found that ginger did not show drug-herb interactions with warfarin when administered to healthy male subjects at the doses recommended in the German Commission E Monographs. (See HC 070554-295)

—Marissa N. Oppel, MS

The American Botanical Council has chosen not to reprint the original article.