

Drug Interaction Report

Patient: CF URI test **Date:** 01/30/2012 14:58

Warfarin Sodium with Food

Onset: Delayed **Severity:** Major **Documentation:** Probable

Warfarin Sodium

Member of interaction class: Anticoagulants
Interacting Ingredient(s): Warfarin

Food

Member of interaction class: Food
Interacting Ingredient(s): Food

Effect: Hypoprothrombinemic effects of Warfarin Sodium may be decreased by vitamin K-enriched foods or increased by grapefruit or cranberry juice.

Mechanism: Large quantities of vitamin K from food may competitively inhibit Warfarin Sodium binding on end-organ cell receptors. Grapefruit juice, and possibly cranberry juice, may inhibit intestinal cytochrome P450 3A4 and increase the bioavailability of warfarin.

Management: All patients receiving Warfarin Sodium should be advised to avoid abrupt changes in dietary vitamin K content. Large quantities of grapefruit juice or cranberry juice should be avoided. Strict vegetarian diets should be avoided. Monitor international normalized ratio and adjust warfarin dosage accordingly.

Discussion: Acquired warfarin resistance has been linked to high or irregular intake of vitamin K (VK) (2,6). Two studies have found high intake of VK or VK-rich foods for 1, 2, or 7 days interfered with anticoagulation therapy (5,10). Case reports have shown changes in anticoagulant effect in patients on stable warfarin who began consuming more VK-rich foods (3,4,8,15,18,19). One study showed that a diet rich in brussel sprouts stimulated warfarin elimination (7); another showed that food decreased the rate, but not extent, of warfarin absorption (1). In 2 case reports, avocado, although low in VK, decreases the effects of warfarin (9). A 44-year-old white male with stable INR had an abrupt decrease of INR from 3.8 to 1.37 (12). He had recently started drinking at least 1/2 gallon of green tea daily. After stopping green tea, INR increased to 2.6. Green teas may contain large quantities of VK (13). INR values in a 70-year-old man on stable warfarin for 7 months decreased from 2.5 to 1.6 after 4 weeks of soy milk and no other dietary or drug changes (17). The effect of frozen grapefruit juice (GJ) on PT in 9 patients on stable warfarin doses was studied (11). Patients ingested 240 ml of GJ 3 times/day for 1 week while taking warfarin. There was no significant difference in PT or INR in any patient(11). In a separate randomized crossover study of 24 patients on routine doses of warfarin (14), the frequency of dose adjustments in a GJ versus orange juice group were similar. Grapefruit Seed Extract (GSE) products have been shown to increase INR (29). Mango has been reported to increase INR in 13 patients by an average of 38% (16). Nineteen cases (20,22,24,25,27,28,31,38) indicate that increases in INR and death (31) have occurred in patients on warfarin who ingested cranberry juice (CJ) or cranberry sauce (30). In contrast, 3 well controlled studies have found 250 ml of CJ once to twice daily for 7 to 14 days does not affect the plasma warfarin concentration, PT, and/or INR (26,32,37). Caution is advised against drinking large quantities of CJ; however, questions remain regarding the validity of the scientific conclusions being extrapolated to moderate amounts of cranberry juice ingestion (36). An INR increase has been demonstrated in a patient taking fish oil (21) and pomegranate juice (33,34), and maitake (35) while decreased warfarin effect has been reported with high-protein, low carbohydrate diets (23).

References: 1. Musa MN et al: CURR THER RES 20:630(1976). 2. Kelly JG et al: Clin Pharmacokinet 4:1(1979). 3. Qureshi GD et al: Arch Intern Med 141:507(1981). 4. Walker FB: Arch Intern Med 144:2089(1984). 5. Karlson B et al: Acta Med Scand 220:347(1986). 6. Kearns PJ et al: JPEN 10:100(1986). 7. Ovesen L et al: Eur J Clin Pharmacol 33:521(1988). 8. Chow WH et al: Postgrad Med J 66:855(1990). 9. Blickstein D et al: Lancet 337:914(1991). <letter> 10. Pedersen FM et al: J Intern Med 229:517(1991). 11. Sullivan DM et al: Am J Health-Syst Pharm 55:1581(1998). 12. Taylor JR et al: Ann Pharmacother 33:426(1999). 13. Booth SL et al: J Agric Food Chem 43:1574(1995). 14. Dresser GK et al: Clin Pharmacol Ther 65:193(1999). <abstract> 15. Bartle WR et al: Am J Health-Syst Pharm 58:2300(2001). <letter> 16. Monterrey-Rodriguez J et al: Ann Pharmacother 36:940(2002). <letter> 17. Cambria-Kiely JA: Ann Pharmacother 36:1893(2002). 18. Kudo T: Artery 17:189(1990). 19. Ohkawa S et al: Rinsho Shinkeigaku 35:806(1995). 20. Suvarna R et al: Br Med J 327:1454(2003). 21. Buckley MS et al: Ann Pharmacother 38:50(2004). 22. Grant P: J Heart Valve Dis 13:25(2004). 23. Beatty SJ et al: Ann Pharmacother 29:744(2005). 24. Sylvan L et al: Am Fam Physician 72:1000(2005). <letter> 25. Rindone JP et al: Am J Ther 13:283(2005). 26. Zhaoping Li et al: J Am Diet Assoc 106:12(2006). 27. Welch JM et al: J Pharm Technol 23:104(2007). 28. Paeng CH et al: Clin Ther 29:1730(2007). 29. Brandin H et al: Eur J Clin Pharmacol 63:565(2007). 30. Mergenhagen KA et al: Am J Health Syst Pharm 65:2113(2008). 31. Griffiths AP et al: J R Soc Health 128:324(2008). 32. Ansell J et al: J Clin Pharmacol 49:824(2009). 33. Komperda KE: Pharmacotherapy 29:1002(2009). 34. Jarvis S et al: Emerg Med J 27:74(2010). 35. Hanselin MR: Ann Pharmacother 44:223(2010). 36. Zikria J et al: Am J Med 123:384(2010). 37. Mellen CK et al: Br J Clin Pharmacol 70:139(2010). 38. Hamann GL et al: Ann Pharmacother 45:e17(2011).

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