



Challenges of Treating Patients with Warfarin

For the past 50 years, the mainstay of anticoagulation therapy has been warfarin.¹ Patient variability in drug metabolism, vitamin K in the diet, and drug interactions create a challenge for prescribers to achieve therapeutic blood levels. According to Jones et al., in spite of frequent monitoring and dose adjustments, patients taking warfarin spend about a third of the time outside the target therapy range.²

In the past year, there were 12,589 warfarin prescriptions filled for 1,604 Nebraska Medicaid patients. In the fiscal year of 2009, there were 11,577 drug interaction alerts addressed by pharmacists for these Medicaid patients.

Warfarin is commonly used for the following conditions³:

- Treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE)
- Prophylaxis of DVT
- Arterial thromboembolism prophylaxis in patients with mechanical prosthetic heart valves
- Cardioembolic stroke prophylaxis in patients with atrial fibrillation (AF)
- Stroke prophylaxis in patients with a history of non-cardioembolic ischemic stroke
- Coronary artery thrombosis prophylaxis following acute myocardial infarction

Warfarin exerts its activity by inhibiting the synthesis of vitamin K dependent clotting factors. At therapeutic doses, the production of these clotting factors by the liver is reduced by 30% to 50%.⁴ Breakdown of circulating clotting factors must occur before effects of warfarin are observed. The degradation half life of vitamin K dependent clotting factors varies between 4 and 72 hours, therefore, 3 to 4 days of therapy may need to be administered before a clinical effect of a single dose is achieved.³

The effectiveness of warfarin is influenced by many factors including diet, pharmacogenomics, and drug interactions.

Administration of vitamin K or transfusion of plasma proteins containing clotting factors will reverse the effects of warfarin.³ Vitamin K is commonly found in green leafy vegetables and some vegetable oils. Broccoli, kale, spinach and lettuces are a source of vitamin K along with olive, soybean and canola oil. Patients are advised to consume no more than an adequate intake of dietary vitamin K to avoid fluctuations in the international ionized ratio (INR).⁵ One study by deAssis et al. demonstrated success in managing a patient's INR by varying the intake of foods rich in vitamin K.⁶

Warfarin is largely eliminated by hepatic metabolism, specifically by cytochrome P450 enzymes. Warfarin is a racemic mixture. The more active S-enantiomer of warfarin is metabolized by CYP2C9 which is a polymorphic enzyme. In vitro, the two variant alleles, CYP2C9*2 and CYP2C9*3 have been shown to decrease metabolism of warfarin and thus increase bleeding risk. Patients carrying the CYP2C9*2 allele required a 17% lower warfarin dose than those patients not carrying the allele. The patients identified as carriers of the CYP2C9*3 allele required a 34% lower warfarin dose than those patients who were not carriers.⁷

Warfarin also reduces the regeneration of vitamin K from vitamin K epoxide by inhibiting the enzyme vitamin K epoxide reductase. There are also variations in the gene which controls production of vitamin K epoxide reductase (VKORC1) which have been associated with lower dose requirements of warfarin. In one study, about 30% of the variance in the dose of warfarin was attributed to variation in the VKORC1 gene. About 40% of the variance in dose was attributed to variations in VKORC1 in combination with the CYP2C9 genotypes.⁸

There are many drug interactions listed in the prescribing information for warfarin, but few controlled trials show clinical significance. The mechanisms of drug interactions

with warfarin may be attributed to CYP450 enzymes, changes in protein binding or changes in coagulation factor synthesis. As noted above, the S-enantiomer of warfarin is metabolized by CYP2C9. Drugs that inhibit CYP2C9, including sulfamethoxazole/trimethoprim (also known as cotrimoxazole or Bactrim) and ciprofloxacin will decrease warfarin metabolism and increase the risk of bleeding. A four-fold increase in the risk of hospitalization for an upper gastrointestinal tract hemorrhage was observed in patients taking warfarin with cotrimoxazole. Treatment with ciprofloxacin in patients taking warfarin was associated with almost a two-fold risk for upper gastrointestinal tract hemorrhage.⁹ Antibiotics may also interfere with warfarin by reducing the vitamin K-producing bacteria in the gut.¹⁰

One of the most clinically significant drug interactions with warfarin is amiodarone. Amiodarone inhibits CYP2C9 and may prolong INR causing an increased risk of hemorrhagic events. Both drugs take several weeks to achieve steady-state, so the onset of the interaction between amiodarone and warfarin may be delayed.¹¹

In addition to their antiplatelet properties, nonsteroidal anti-inflammatory drugs (NSAIDs) are highly protein bound, as is warfarin. NSAIDs are also metabolized by the CYP450 isoenzymes. In a retrospective case control study, 39.8% of patients using warfarin had an increase in INR when an NSAID was initiated.¹²

Medicating a patient with therapeutic doses of warfarin alone can increase bleeding risk. In 5 randomized, controlled trials in patients with non-rheumatic AF the incidence of major bleeding was between 0.5% and 2.7%.⁴ Many factors can influence warfarin's effect on INR including disease states, advanced age, and possible warfarin resistance.

Patients taking warfarin should be monitored frequently, as many factors can influence the INR. Coordination of care is especially important for patients taking warfarin. A claims analysis which examined the relationship between warfarin use and the risk of hemorrhage showed that the likelihood of hemorrhage is greater for patients who were receiving prescriptions from multiple prescribers.¹³

References

1. Ansell J, Buttaro M, Thomas O, Knowlton C. Consensus guidelines for coordinated outpatient oral anticoagulation therapy management: Anticoagulation Guidelines Task Force. *Ann Pharmacother.* 1997;31:604-615.
2. Jones M, McEwan P, Morgan C, Peters J, Goodfellow J, Currie C. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. *Heart.* 2005;91(4):472-477.
3. Clinical Pharmacology Web site. <http://www.clinicalpharmacology-ip.com.library1.unmc.edu:2048/Forms/Monograph/monograph.aspx?cpnum=650&sec=mondesc>. Accessed June 14, 2010.
4. Coumadin (Prescribing Information) Bristol-Myers Squibb January 2010.
5. Booth S. Dietary vitamin K guidance: an effective strategy for stable control of oral anticoagulation? *Nutrition Reviews.* 2010; 68(3):178-181.
6. deAssis M, Rabelo E, Avila C, Planczyk C, Rohde L. Improved Oral Anticoagulation After a Dietary Vitamin K-Guided Strategy. *Circulation.* 2009;120:115-1122.
7. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose and bleeding risk in warfarin-treated patients: A HUGenet systemic review and meta-analysis. *Genet Med.* 2005;7:97-104.
8. Wadelius M, Chen L, Downes K, et al. Common VKORC1 and GGX polymorphisms associated with warfarin dose. *Pharmacogenomics J.* 2005;5:262-270.
9. Fischer H, Juurlink D, Mamdani M, Kopp A, Laupacis A. *Arch Intern Med.* 2010;170(7):617-621.
10. Schelleman H, Bilker W, Brensinger C et al. Warfarin-Fluoroquinolones, Sulfonamides, or Azole Antifungals Interactions and the Risk of Hospitalization for Gastrointestinal Bleeding. *Clin Pharmacol Ther.* 2008 November;84(5):581-588.
11. Edwin S, Jennings D, Kalus J. An Evaluation of the Early Pharmacodynamic Response After Simultaneous Initiation of Warfarin and Amiodarone. *J Clin Pharmacol.* 2010;50:693-698.
12. Choi K, Kim A, Son I et al. Risk Factors of Drug Interaction between Warfarin and Nonsteroidal Anti-Inflammatory Drugs in Practical Setting. *J Korean Med Sci.* 2010;25:337-341.
13. Zhang K, Young C, Berger J. Administrative Claims Analysis of the Relationship Between Warfarin Use and Risk of Hemorrhage Including Drug-Drug and Drug-Disease Interactions. *JMCP.* 2006;12(8):640-648.

NEBRASKA DUR

DUR Director

Marcia Muetting, PharmD, RP
6221 S 58th Street, Suite A
Lincoln, Nebraska 68516
Phone (402) 420-1500
Fax (402) 420-1406
Email dur@npharm.org
Website www.durnebraska.org

Nebraska Medicaid

Health & Human Services
PO Box 95026
Lincoln, Nebraska 68509-5026
Phone (402) 471-9029
Fax (402) 471-9092
Email medicaid.pharmacy@dhhs.ne.gov
Website www.hhs.state.ne.us/med/medprog.htm