# Warfarin Drug Interactions: The Role of Genetics

John R. Horn, PharmD, FCCP, and Phillip D. Hansten, PharmD

*Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.*

This column has reviewed the general influence of genetic-based differences in drug-metabolizing activity on drug interactions (see the September 2006 issue of *Pharmacy Times* or visit www.PharmacyTimes.com/genetics). The metabolism of codeine, timolol, propranolol, and metoprolol is determined by CYP2D6, while the metabolism of several proton pump inhibitors is markedly affected by CYP2C19 activity. In addition to CYP2D6 and CYP2C19, CYP2C9 activity varies among individuals based on their genetics. CYP2C9 is the primary pathway for the metabolism of nonsteroidal anti-inflammatory agents, tolbutamide (Orinase), glyburide (DiaBeta), glipizide (Glucotrol), and warfarin (Coumadin). Warfarin is a drug with a narrow therapeutic range and represents numerous potential drug interactions that can result from pharmacokinetic or pharmacodynamic mechanisms.[1-3] The interactions based on both of these mechanisms can be influenced by a patient's genetic makeup.

Pharmacokinetic interactions with warfarin can alter its absorption, distribution, or elimination. Interactions affecting warfarin metabolism are the most susceptible to genetic influence. Specifically, several cytochrome P450 (CYP450) enzymes, including CYP2C9, CYP3A4, CYP1A2, and CYP2C19, contribute to the elimination of warfarin. While the activity of both CYP2C19 and CYP2C9 are genetically determined, CYP2C9 is more important because it is the primary pathway for the elimination of S-warfarin, the warfarin enantiomer considered to be the most potent anticoagulant. Drugs that inhibit the activity of CYP2C9 (eg, sulfamethoxazole/trimethoprim [Bactrim], fluconazole [Diflucan], amiodarone [Cordarone], fluvastatin [Lescol], simvastatin [Zocor], lovastatin [Mevacor], and voriconazole [Vfend]), will increase the plasma concentration of warfarin and its therapeutic effect. Some patients (6%-8%) have genetic polymorphisms that result in reduced CYP2C9 activity, however. They are referred to as poor metabolizers (PMs) for CYP2C9.

Patients who are PMs for warfarin metabolize the drug more slowly and often require smaller doses of warfarin to achieve therapeutic international normalized ratio values. These patients tend to be at higher risk of serious side effects than patients without the genetic variant. Because PMs have minimal CYP2C9 activity, however, drugs that can inhibit CYP2C9 will have only a small effect on warfarin response. Simply stated, when a patient has little or no enzyme activity, there is little or no enzyme activity to inhibit. Thus, PMs for CYP2C9 are protected from common drug interactions with warfarin resulting from CYP2C9 inhibitors. Because their primary pathway of warfarin elimination is inhibited, these patients depend to a greater extent on the other pathways of elimination and may be more sensitive to inhibitors of CYP3A4, CYP1A2, or CYP2C19.

Warfarin produces its therapeutic effect by inhibiting the action of vitamin K epoxide reductase complex 1 (VKORC1) that is necessary to produce the clotting factors II (prothrombin), VII, IX, and X. Like CYP2C9, several genetic polymorphisms of VKORC1 can alter a patient's response to warfarin.[4] Patients who have genetically determined VKORC1 that does not function normally are more sensitive to the effects of warfarin. Thus, having a genetic polymorphism that results in reduced VKORC1 function will increase a patient's sensitivity to warfarin. Likewise, these patients may be at increased risk from drug interactions that increase warfarin plasma concentrations because their VKORC1 does not function normally to produce vitamin K–dependent clotting factors.

It is possible that some patients, based on their VKORC1 genotype, will be more susceptible to changes in vitamin K intake or drugs that alter vitamin K absorption or production (eg, antibiotics). A better understanding of variations in VKORC1 activity will be helpful in predicting the magnitude of effect seen with agents affecting vitamin K.

For patients, the combination of their CYP2C9 and VKORC1 genotype will influence their response to warfarin. The changes in warfarin response during concomitant administration of interacting drugs also will be affected by these genetic differences. More studies will be required to assess which patients are more or less likely to exhibit exaggerated responses to drugs that interact with warfarin metabolism. While the therapeutic range of oral hypoglycemic agents is wider than that of warfarin, genetic differences in CYP2C9 activity may also modify the risk of adverse events in patients with diabetes taking hypoglycemic agents and CYP2C9 inhibitors. Patients with extensive CYP2C9 activity, who are administered an inhibitor such as sulfamethoxazole, may be at greater risk for developing hypoglycemia than patients who are PMs for CYP2C9. PT

*For a list of references, go to: www.PharmacyTimes.com.*