Pharmacogenomic Considerations for Customizing Warfarin Therapy in the Orthopedic Patient

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Patients undergoing orthopedic surgery including knee replacement, hip replacement, and hip fracture surgery are at increased risk for venous thromboembolism, including deep venous thrombosis (DVT) or pulmonary embolism, due to venous injury and decreased mobility. Although these patients typically receive venous thromboembolism prophylaxis in the form of unfractionated heparin or low-molecular-weight heparin in the immediate postoperative period; up to 10% will develop a venous thromboembolism within 3 months postoperatively.1 When this occurs, patients often are anticoagulated with a vitamin K antagonist, warfarin. Warfarin therapy is complicated by the fact that it has a narrow therapeutic index and requires monitoring of the international normalized ratio to target a range between 2.0 and 3.0 in orthopedic surgery patients.1 Response to warfarin therapy is affected by individual patient factors such as other medication use, disease states, diet, and genetic variations. In particular, genetic variations on cytochrome P450 2C9 (CYP2C9), an enzyme found in the liver, and vitamin K epoxide reductase complex 1 gene (VKORC1) have been identified to contribute to inconsistencies in warfarin dose response. Certain variations can predict a patient’s sensitivity to warfarin and provide practitioners with information on initial and ongoing dosing recommendations to maintain international normalized ratios within the therapeutic range. The increasing availability of genetic tests for detecting these variations is allowing for a more accurate and customized method of dosing warfarin.

GENETIC VARIATIONS IN CYP2C9 AND VKORC1

The anticoagulation caused by warfarin is due to the inhibition of vitamin K epoxide reductase. Vitamin K epoxide reductase is an enzyme that activates vitamin K to make clotting factors II, VII, IX, and X. (S)-warfarin, the more potent enantiomer of the warfarin racemic mixture, is metabolized by the enzyme, CYP2C9. Single nucleotide polymorphisms on the CYP2C9 gene create variant alleles that have been found to reduce the activity of CYP2C9, thus decreasing warfarin’s clearance. When compared to the wild type allele CYP2C9*1, the variant allele CYP2C9*2 decreases clearance by approximately 30% and CYP2C9*3 decreases clearance by approximately 80%.2 This results in patients with wild type alleles, CYP2C9*1/*1, requiring a daily mean maintenance warfarin dose that is higher than what is required for CYP2C9*1/*2 heterozygotes and CYP2C9*1/*3 heterozygotes, with the latter requiring the lowest dose (Figure 1).2 The frequency of the variant alleles differs depending on race, with CYP2C9*2 and CYP2C9*3 being more common in European Americans at 12% and 8%, respectively, and less common in Asians and African Americans.3 Genetic variations on VKORC1, the gene responsible for encoding vitamin K epoxide reductase, have also...
been found to affect warfarin therapy. Five VKORC1 haplotypes (H1, H2, H7, H8, and H9) affecting warfarin dose requirements have been identified to occur in patients at a frequency >5%. The haplotypes were associated with altered expression of messenger ribonucleic acid, the molecule required for the synthesis of proteins producing VKORC1. Expression of messenger ribonucleic acid was decreased in Group A haplotypes, leading to a lower dose requirement while Group B haplotypes were associated with increased messenger RNA expression and may explain why some patients require higher doses of warfarin.

Rieder et al found the A/A haplotype combination required a daily warfarin dose that was lower than the dose required for the A/B haplotype, and the A/B haplotype required a dose that was lower than the B/B haplotype (Figure 2). As with the CYP2C9 variant alleles, the frequency of VKORC1 haplotypes also varies depending on race. The frequency of Group A haplotypes was 89% in Asians, 14% in African Americans, and 37% in European Americans.

The combination of the genetic variations on CYP2C9 and VKORC1, and other potentially undiscovered variations, has led to the complexity seen with warfarin dosing. As a result, the FDA approved an addition to the warfarin manufacturer labeling in 2007. It includes information from pharmacogenomic studies suggesting that there is an increased risk of bleeding in patients who have either the CYP2C9*2 or CYP2C9*3 allele. In addition to this warning, the package insert now states that polymorphisms in CYP2C9 and VKORC1 contribute to 40% of the variance in warfarin dosing. The new labeling suggests genetic testing in patients to assist with dosing and decrease the risk of bleeding, but it does not require it.

**EFFECT OF GENETIC VARIATIONS ON DOSING**

Currently, warfarin is empirically dosed using clinical information based on patient factors such as nutritional status, hepatic impairment, age, and use of other medications. The anticoagulant is typically initiated in doses ranging from 2.5 to 10 mg daily (average, 5 mg daily), which are then adjusted based on international normalized ratio to meet the patient’s therapeutic goal. The risk of bleeding is greatest during the first 3 months of therapy because achieving the goal international normalized ratio may require frequent adjustment of dose, potentially leading to overanticoagulation.

With genetic testing, the initial dose required for individual patients may be determined more accurately without trial and error.

The International Warfarin Pharmacogenetics Consortium conducted a study in which warfarin, dosed using a pharmacogenetic dosing algorithm, was compared to a fixed dose of 5 mg/day and also to a dosing algorithm only based on clinical factors. DNA samples were used to genotype for both CYP2C9*2 and CYP2C9*3 single nucleotide polymorphisms and VKORC1 haplotypes. Patients were assessed to determine the percent of warfarin doses predicted within 20% of the therapeutic dose that would result in an international normalized ratio between 2.0 and 3.0. Further classification into patients requiring a low dose (<21 mg/week), intermediate dose (≥21 and <49 mg/week), and high dose (≥49 mg/week) was done for assessment. Results showed that specifically for the low dose and high dose groups, the pharmacogenetic dosing algorithm predicted doses that were more accurate than doses from the clinical dosing algorithm and the fixed-dose approach. Accuracy of dosing using the 3 approaches was similar in the intermediate dose group. The number needed to genotype for a dose estimate within 20% of the required dose was also calculated; 1 in 13.2 patients was the number needed to genotype for dose estimation in the clinical dosing algorithm group and 1 in 6.0 in the fixed-dosing group. The use of pharmacogenetic information produced a more accurate method of determining initial dose of warfarin, but whether accurate initial dosing is clinically significant cannot be determined from this study.

Several studies have examined clinically relevant outcomes such as time to stable
Genetic variations on CYP2C9 and VKORC1 are responsible for 40% of variance in warfarin dosing.

Recent changes to warfarin labeling include the addition of pharmacogenomic information recommending the use of genetic testing prior to initiation of warfarin. However, more research is needed in racially diverse populations.

Current evidence suggests genetic testing may improve warfarin therapy in orthopedic surgery patients by increasing the time spent in therapeutic international normalized ratio range and by decreasing the incidence of adverse events.

More research is needed to fully determine the clinical impact of genetic testing in patients initiated on warfarin therapy.

While genetic variations lead to inconsistencies in initial dosing requirements, it is unknown yet if these inconsistencies are significant in terms of causing adverse effects such as bleeding.

Higashi et al performed a retrospective cohort study measuring time to serious and life-threatening bleeding events to determine if differences in time to therapeutic international normalized ratio, time to stable warfarin dose, and rate of above-range international normalized ratio translate to bleeding risk. Patients were determined to have wild type genotype (*1/*1) or variant genotypes (*1/*2, *1/*3, *2/*2, *2/*3, *3/*3). Bleeding events were found to be more frequent in patients with variant alleles, as the rate of serious and life-threatening bleeding events was 10.92 and 1.56 per 100 patient years respectively. In the wild type group, the rate was 4.89 and 0.70 per 100 patient years for serious and life-threatening bleeding events, respectively. It is important to note that although increased international normalized ratio may lead to bleeding events, this is not always the case, and increased international normalized ratio should be differentiated from bleeding events to determine the true clinical effects of these genetic variations.

Genetic testing allows the option for therapy with certain medications such as warfarin to be altered to meet specific patients’ needs. There are several genetic tests for warfarin that have been approved by the Food and Drug Administration (FDA) and are commercially available. Performing the test can take as little as 24 hours but obtaining the results may take longer. The cost of a test may range between $200 to $400.

While use of genetic information may be beneficial in decreasing time to therapeutic dose and bleeding risks, some worry that it may cause health care professionals to underestimate the need for monitoring international normalized ratio. Because warfarin has a narrow therapeutic index and many other factors affect dose requirements other than genetic variations on CYP2C9 and VKORC1, international normalized ratio measurement is still necessary.

There are also ethical and legal issues associated with testing and using genetic information. Knowledge of genetic variations may alter treatment plans and whether it will lead to a better outcome is difficult to determine.

Health care professionals must consider other factors that affect the efficacy of warfarin along with the reliability of the genetic test. It may also be a challenge to distinguish which patients may benefit from genetic testing. This decision must be based on scientific evidence to avoid genetic profiling.

If a prescriber disregards the possibility for genetic variations present in a patient and a bleeding event occurs, it is possible the patient may take legal action against the clinician. Similarly, insurance companies may be held liable if adverse events result from denying coverage of genetic tests.

Clinical Impact in Orthopedic Surgery Patients

Current evidence suggests that certain genetic variations on CYP2C9 and VKORC1 are associated with increased international normalized ratios and perhaps clinically significant bleeding events; therefore the use of pharmacogenetic information in determining the proper warfarin dose may aid in decreasing the risk of bleeding events. Lenzini et al conducted a study focusing specifically on the clinical impact pharmacogenetic-based dosing may have on orthopedic surgery patients. In this nonrandomized, prospective study, results indicated that genetic testing may be useful in optimizing warfarin therapy. Patients spent a longer duration of time in the therapeutic international normalized ratio range and experienced fewer adverse events when results from genetic testing were used for dose adjustment after 4 doses of warfarin had previously been administered.

Despite the increasing availability of genetic testing, approximately 2% of physicians use genetic tests for warfarin therapy. Perhaps this is due to the need for more information about the pharmaco-economic impact of genetic testing. To determine if genetic testing
for warfarin therapy is cost effective, factors relating to the genetic test, the target gene, the clinical outcome if testing is not initiated, and the treatment options based on testing outcome must be considered. The cost of a bleeding event is an estimated $5,500, while the cost for genetic testing is $200. The annual risk of major bleeding and major bleeding resulting in death is approximately 8% and 1%, respectively, although the relative risk of a bleeding event in the estimated 30% of patients with a variant allele on CYP2C9 is 2.5. Veenstra and Carlson evaluated the pharmacoeconomics of genetic testing using a decision analysis and found a 1.24% and 0.0124% decrease in risk of bleeding and death, respectively, although the relative risk of a bleeding event in the estimated 8% and 1%, respectively, although the relative risk of a bleeding event in the estimated 30% of patients with a variant allele on CYP2C9 is 2.5. Veenstra and Carlson evaluated the pharmacoeconomics of genetic testing using a decision analysis and found a 1.24% and 0.0124% decrease in risk of bleeding and death, respectively, although the relative risk of a bleeding event in the estimated 8% and 1%, respectively, although the relative risk of a bleeding event in the estimated 30% of patients with a variant allele on CYP2C9 is 2.5.

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