EDITORIALS

Personalizing Health Care—Is This the Right Time for Warfarin?

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"The Secretary of the Department of Health and Human Services…has identified personalized health care as one of the Department's top priorities, and pharmacogenetics is an important component of making health care more personalized."[1] This statement, from an employee of the FDA, coincides with the change in labeling for warfarin therapy, which stated that: "…lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1…"[2] Although the statement seems relatively innocuous, it raises the question of whether physicians should be determining an individual's genotype before proceeding with warfarin therapy. The importance of pharmacogenetics or pharmacogenomics cannot be denied as evidenced by examples of other drugs whose altered metabolism results in important clinical outcomes or where genetic mutations influence a response to a specific therapy.[3–5] But was this change in labeling for warfarin therapy a rush to judgment on the part of the FDA to fulfill its goal of advancing personalized medicine or a proper response to the available data?

Warfarin is a stereo isomer of two enantiomers, the S enantiomer having the principal biologic effect of interfering with vitamin K metabolism (Fig. 1).[6] S-warfarin is metabolized by the P450 cytochrome oxidase, 2C9. Two relatively common single nucleotide polymorphisms are responsible for altering the metabolic function of CYP2C9 leading to impaired drug metabolism, accumulation of warfarin, and further elevation of the INR. Warfarin's major target is the vitamin K oxide reductase complex 1 (VKORC1). Several polymorphisms in combination lead to haplotypes with either enhanced or reduced sensitivity to warfarin. In addition to genetic factors that affect warfarin's pharmacokinetic and pharmacodynamic behavior, warfarin effect is also influenced by age, gender, body surface area, dietary vitamin K content, liver function, and multiple drug interactions. Thus, pharmacogenetic-based dosing by itself is not a solution to improved therapeutic effectiveness, but must be considered along with these other factors. Complex dosing equations, some of which are freely available on the web, incorporate many of these factors.[7]

Warfarin may seem like the "poster child" for pharmacogenetic dose management. Its pharmacokinetics are well characterized; the gene encoding for its major metabolic enzyme has been identified; numerous single nucleotide polymorphisms (SNPs) have been described, manifesting impaired warfarin metabolism.[8] Warfarin's pharmacodynamics have also been elucidated with the gene encoding for its enzymatic target recently identified[9], and numerous haplotypes described resulting in enhanced or impaired sensitivity to warfarin.[10] In the span of less than 10 years multiple retrospective analyses have also described the frequency of genetic variants in ethnic populations and correlated genetic variants with altered dose requirements as well as bleeding complications. Warfarin dosing, however, is different from all other medications (except unfractionated heparin) in that it requires intense dose monitoring to maintain a therapeutic effect, and it has a simple assay to determine the effect (i.e., the prothrombin time expressed as the International Normalized Ratio or INR). One must then address several questions: (1) Does pharmacogenetic-based dosing add any additional value to INR monitoring, such as fewer adverse events, more rapid achievement of therapeutic anticoagulation, shorter hospitalizations, or less frequent INR monitoring; (2) if so, is the additional cost of pharmacogenetic-based dosing worth the additional benefit; (3) is access to pharmacogenetic testing practical at this time.

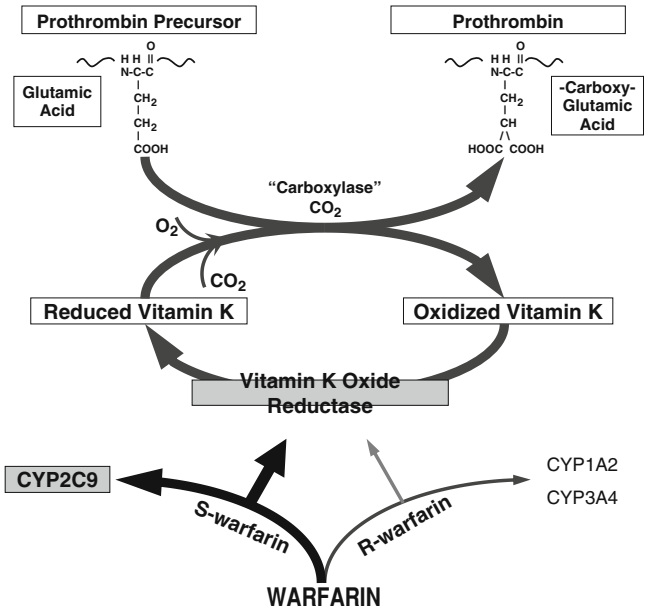

Figure 1. The interrelationships between vitamin K, coagulation factors, and warfarin. Prothrombin, representative of the vitamin K-dependent coagulation factors (II, VII, IX, and X), requires reduced vitamin K to become fully functional. Vitamin K is oxidized and then recycled. S-warfarin's pharmacologic effect is mediated by interfering with the vitamin K oxide reductase enzyme and the recycling of vitamin K. S-warfarin is metabolized by P450 enzyme CYP2C9.

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Only recently have prospective randomized trials attempted to assess some of these outcome parameters.

Kangelaris et al.[11], in this issue of the Journal, perform a systematic review of randomized, controlled trials of pharmacogenetic-based dosing of warfarin. They quickly discover several facts: of over 1,700 citations on the topic, there are only 3 randomized, controlled trials; of these trials, not only are their designs less than ideal, the trials are underpowered to yield the important outcomes of interest, and there is such heterogeneity between the trials that making unified conclusions is difficult. Most problematic is that the intervention arm of each trial is considerably different. One trial incorporates CYP2C9 and VKORC1 genetic data, along with age, weight, gender, and amiodarone use into their algorithm; another uses six different algorithms based on CYP2C9 genetic data with modifications based on amiodarone use; the third uses CYP2C9 data along with age, body surface area, the presence or absence of a heart valve, diabetes, and other factors. The authors found no statistically significant difference in bleeding rates or time within the therapeutic INR range, and they concluded that there was insufficient evidence to support pharmacogenetic-based warfarin dosing at this time. If the outcome had been positive, what would the practicing physician take away from this analysis? What algorithm is preferred? How would one use the complicated formulas required? Is the genetic test available on a timely basis? Is the cost of testing worth the potential benefit?

This last question was recently addressed by Eckman et al.[12] using data from the literature and applying it to a hypothetical case of atrial fibrillation. They found that genotyping was unlikely to be cost effective for the average patient, but may be cost effective (< $50,000 per quality adjusted life year) for patients with a high risk of hemorrhage who are starting therapy. In the current issue of the Journal, Eckman et al.[13] further analyze the question of cost effectiveness by asking the interesting question of whether treatment decisions for patients with atrial fibrillation (AF) based on a risk/benefit analysis can be enhanced by knowledge of CYP2C9 culprit alleles for impaired enzyme function that are reported to be associated with increased bleeding. In other words, they further enhance the bleeding risk assessment side of the equation by factoring in the presence or absence of a variant CYP2C9 enzyme. The authors develop a Markov decision model based on an average risk case of AF and use data from the literature based entirely on retrospective reports of increased bleeding with CYP2C9 alleles resulting in enzymes with reduced function. The premise is that if the risk of stroke is low (but not necessarily low enough to exclude warfarin as the treatment of choice), and the risk of bleeding high due to possession of a culprit allele, then treatment with aspirin (associated with a lower risk of drug-induced bleeding) has greater value than warfarin. However, prospective data have yet to confirm the increased bleeding seen in retrospective reports, nor is it clear what the increased bleeding is due to, other than unstable or non-therapeutic INRs. It is difficult to accept the premise that acquiring such knowledge would lead one to use a less effective therapy, rather than using that knowledge to guide the physician towards more intense INR monitoring, which might abrogate the risk of bleeding.[14]

Further complicating this issue is the recent study by Klein et al.[15] showing, retrospectively, in a large international cohort of patients that a pharmacogenetic-based dose algorithm predicted the therapeutic dose better than a clinical algorithm only for patients taking ≤21 mg/week or ≥49 mg/week, neither of which would be known to a practitioner prior to dosing a patient.

What then does the clinician need to know about pharmacogenetic-based dosing of warfarin therapy? First, well-designed, prospective, randomized trials of pharmacogenetic-based dosing of warfarin therapy large enough to yield important outcomes have not been done. Second, the few small studies that have been completed are poorly designed, are quite heterogeneous, and have shown mixed results in achieving a therapeutic range faster or increasing time in range. Third, cost effectiveness studies using retrospective outcome data and hypothetical case scenarios have not shown testing to be generally cost effective. Lastly, pharmacogenetic-based dosing is not simple; it requires timely acquisition of genetic assays and the use of complex dosing formulas. This does not mean that properly designed studies should not be done, only that it is too early to recommend such testing. A recently funded NIH study[16] may answer some of the these questions, but even this study is not projected to be large enough to address whether or not pharmacogenetic-based dosing will lead to fewer major bleeds or thrombotic episodes compared to good INR-based dose management.

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REFERENCES

1. **Gage BF, Lesko LJ.** Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. J Thromb Thrombolysis. 2008; 25: 45–51.
2. http://packageinserts.bms.com/pi/pi_coumadin.pdf
3. **Weinshilboum R.** Inheritance and drug response. N Engl J Med. 2003; 348: 529–37.
4. **Mega JL, Close SL, Wivott SD, et al.** Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009; 360: 354–62.
5. **Yang JJ, Cheng C, Yang W, et al.** Genome-wide interrogation of germline genetic variation associated with treatment response in childhood acute lymphoblastic leukemia. JAMA. 2009; 301: 393–403.
6. **Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G.** The pharmacology and management of the vitamin K antagonists: ACCP evidence-based clinical practice guidelines. Chest. 2008; 133: 160S–198S.
7. www.warfarindosing.org
8. **Beinema M, Brouwers RBJ, Schalekamp T, Wilffert B.** Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. Thromb Haemost. 2008; 100: 1052–57.
9. **Li T, Chang CY, Jin DY, et al.** Identification of the gene for vitamin K epoxide reductase. Nature. 2004; 427: 541–4.
10. **Rieder MJ, Reiner AP, Gage FB, et al.** Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005; 352: 2285–93.
11. **Kangelaris KN, Bent S, Nussbaum RL, Garcia DA, Tice JA.** Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. J Gen Intern Med. 2009.
12. **Eckman MH, Rosand J, Greenberg SM, Gage BF.** Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med. 2009; 150: 73–83.
13. **Eckman MH, Greenberg SM, Rosand J.** Should we test for CYP2C9 before initiating anticoagulant therapy in patients with atrial fibrillation? J Gen Intern Med. 2009.
14. **You JHS, Chan FWH, Wong RSM, Cheng G.** The potential clinical and economic outcomes of pharmacogenetics-oriented management of warfarin therapy-a decision analysis. Thromb Haemost. 2004; 92: 590–7.
15. International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009; 360: 753–64.
16. Clinicaltrials.gov identifier: NCT00839657