Use of Pharmacogenetics in Guiding Treatment with Warfarin

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Warfarin is the most widely used oral anticoagulant for the treatment of thromboembolic disorders and for stroke prophylaxis. Warfarin is a problematic drug because it exhibits large interindividual variation in the required therapeutic dose, has a narrow therapeutic range, and shows multiple food and drug interactions. Its anticoagulant effect is monitored by measuring the international normalized ratio (INR), which is a function of the time required for a patient’s blood to coagulate relative to the time it takes for a reference blood sample. Although warfarin has been used in humans for more than 50 years, its main side effect—bleeding—is a leading cause of hospital admission and drug-related death (1, 2). This problem has made patients and clinicians yearn for a new efficient and safe oral anticoagulant drug that does not require frequent monitoring. In Europe, a new oral anticoagulant drug (dabigatran) claimed to have these qualities has been licensed for short-term primary prevention of venous thromboembolic events, but its effectiveness in long-term secondary thromboprophylaxis remains to be shown. Furthermore, the daily cost of dabigatran is 5 times that of warfarin therapy including INR tests. To switch all warfarin patients (currently 1% of the population in many Western countries) to dabigatran would boost national costs in countries with subsidized drug programs; therefore, national authorities will probably encourage the continued use of warfarin, even when oral thrombin inhibitors become available for long-term thromboprophylaxis.

Given that warfarin is likely to maintain its position as the most widely used oral anticoagulant for the foreseeable future, it is crucial to improve the safety of this drug. The risk of over-anticoagulation and bleeding is especially high before stable anticoagulation has been established. One way to minimize this risk would be to shorten the time to stable anticoagulation by tailoring the initial dose for each patient. The required warfarin dose, which can vary 20-fold among individuals, can be roughly estimated from clinical and demographic factors, such as age, body weight, concurrent disease, and drug and food interactions (3). A number of dosage algorithms that use clinical and demographic factors have been tested and are able to reduce the time to therapeutic anticoagulation (4). More recent discoveries have shown that variation in the genes that encode the main enzyme responsible for S-warfarin metabolism (CYP2C9,2 cytochrome P450, family 2, subfamily C, polypeptide 9) and the target of warfarin (VKORC1, vitamin K epoxide reductase complex, subunit 1) influence dose requirements by affecting pharmacokinetics and pharmacodynamics (5). Polymorphisms in these genes are also associated with the risk of over-anticoagulation during initiation of warfarin therapy (6). A large prospective study on warfarin pharmacogenetics provided probabilities of over-anticoagulation (INR >4) in patients with different CYP2C9 and VKORC1 alleles (Fig. 1) (7). During the first month of treatment, CYP2C9*3/*3 individuals had a 22-fold increased risk of an INR >4 and a tendency for more episodes of serious bleeding compared with individuals with CYP2C9*1/*1. Patients homozygous for VKORC1 variants had a 4.5-fold increased risk of an INR >4 within 5 weeks (7). Genotyping the CYP2C9 and VKORC1 genes could avert overdosing in patients who are warfarin sensitive because of these polymorphisms. Several pharmacogenetic algorithms that predict warfarin maintenance doses have been developed by combining genetic, clinical, and demographic factors with warfarin-dosing data and INR measurements (3). If genetic testing is integrated into routine warfarin therapy, it is estimated that American warfarin users would annually avoid 4500 to 22 000 serious bleeding events (8).

The American regulatory agency, the Food and Drug Administration, decided to update the label of warfarin in 2007 to encourage lower initiation doses in patients with CYP2C9 and VKORC1 variant alleles.

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2 Human genes: CYP2C9, cytochrome P450, family 2, subfamily C, polypeptide 9; VKORC1, vitamin K epoxide reductase complex, subunit 1.
Warfarin thus has the potential to become one of the first drugs in which pharmacogenetic dosing is introduced into routine therapy. It is difficult to predict how routine genotyping would affect US health care costs; predictions range from savings of $357 million to increased costs of $445 million annually. Pharmacogenetic dosing algorithms currently predict approximately 50% of the dose variance in Caucasians, but perform less well in Asians and African Americans and need to be adapted by including additional factors. Furthermore, existing pharmacogenetic algorithms show a poor fit at very high doses because they rely on genetic polymorphisms that increase the sensitivity to warfarin. This situation could be improved by incorporating rarer mutations that cause warfarin resistance into the dose models. Another issue is how to predict loading doses from maintenance-dose models. Finally, it is necessary to test the clinical utility of pharmacogenetic warfarin dosing before its implementation on a broad scale. Two prospective clinical trials of predicted warfarin dosing have shown promising results (9, 10). In the Israeli trial, 95 patients who began warfarin therapy according to their CYP2C9 genotype were compared with 96 patients who received doses according to a clinical algorithm (9). In the American trial, 101 patients who received their initial warfarin treatment according to CYP2C9 and VKORC1 genotypes were compared with 99 patients randomized to standard therapy (10). Despite small sample sizes, both studies claimed that pharmacogenetics increased the efficiency of warfarin initiation. To produce irrefutable results, however, requires adequately powered randomized clinical trials of pharmacogenetic warfarin dosing. Two large clinical trials—one American and one European—of pharmacogenetic vs conventional warfarin initiation are starting in 2009. If the results from these

For most patients, the target INR range is 2–3. An INR >4 indicates an increased risk of bleeding. Figure from Wadelius et al. (7). Used with permission.
trials are encouraging—and previous studies on warfarin pharmacogenetics suggest that they will be—then pharmacogenetic dosing will be ready to be introduced into clinical practice. It is hoped that the implementation of pharmacogenetics will improve the safety and cost-effectiveness of oral anticoagulant treatment. Warfarin’s long era as a leading cause of serious hospital admission and drug-related death could thereby be brought to an end.

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References