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Pharmacogenetics of Warfarin - Should we test?

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Warfarin is the mainstay of anticoagulation therapy. It is used for the prevention and treatment of venous thromboembolism, myocardial infarction, and strokes. Its clinical use, however, is complicated by the fact that it has a narrow therapeutic index with associated adverse effects that are potentially serious, i.e., bleeding, and the dosage requirement to produce a required degree of anticoagulation varies widely between patients. The reason for the latter is multi-factorial and includes determinants such as drugs, age, diet, race and genetic factors. To date, there has been no reliable means of predicting an individual's response to warfarin prior to initiating therapy.

The discovery of common polymorphisms related to warfarin pharmacokinetics and pharmacodynamics over the last 10 years provides a unique opportunity to develop a pharmacogenetics-based approach to oral anticoagulant therapy. By using a pharmaco-genetics-based approach to predict the patient's maintenance dose *a priori,* initiation of warfarin therapy may become safer and more efficient.

In this issue, Sittinateskul and colleagues demonstrate that genetic variations in the vitamin K epoxide reductase *(VKORC1)* and cytochrome P-450 2C9 *(CYP2C9)* genes has an effect on the maintenance dose of warfarin in Thai patients and anticoagulation outcome. These findings suggest a role of clinical testing of these two genes.[1]

As the highest risk of excessive anticoagulation and bleeding is during the initiation of therapy, pharmacogenetics-based warfarin therapy has the potential to reduce the risk of bleeding, shorten the time to stabilization of therapy, and improve the efficiency of initiating warfarin therapy by accurately estimating the warfarin maintenance dose *a priori.* Pharmacogenetics-based warfarin therapy will not obviate the need for INR monitoring or dose adjust-ments. Instead, pharmacogenetics-based therapy may reduce the effort and expense of dose titration during the induction period. Before pharmacogenetics-based warfarin dosing is widely used, the benefits of pharmacogenetics-based dosing should be assessed in a randomized controlled trial against traditional trial and error dosing. Finally, if the trial is successful, the cost-effectiveness of pharmacogenetics-based therapy needs to be assessed.

Reference

1. Sittinateskul P, Angchaisuksir P, Sasanakul W, Chuansumrit A. Genetic Determinants of Response to Warfarin in Thai Patients. Rama Med J. 2009;32:176-85.