Is a “Pharmacogenomic Algorithm” Helpful for Adjusting the Initial Dose of Warfarin in Patients to Be Treated by Warfarin Therapy?

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Recent progress in basic science has proven that both the pharmacokinetics and pharmacodynamics of warfarin are influenced strongly by genetic polymorphism of enzymes relating to its metabolism (Figure). Computer-based dose adjustment, taking the genetic variation of warfarin-metabolizing enzymes into consideration, is expected to be helpful for physicians choosing the initial dose of warfarin.

In this issue of the Journal, Takeuchi et al attempted to clarify the clinical utility of a computer-based algorithm developed by the International Warfarin Pharmacogenetics Consortium for Japanese patients treated with warfarin. Obviously, the model generated by the IWPC is quite simple and includes just a few factors already known to influence the optimal dose of warfarin: age, height, weight, and polymorphism of CYP (cytochrome P450) 2C9 and vitamin K epoxide reductase complex (VKORC). In this model, various unknown genetic heterogeneities between Caucasian and Asian subjects are included, but only as “Asian Race”. With this simple modeling, however, the authors found that the algorithm is still useful for finding specific Japanese patients requiring very low doses of warfarin.

The IWPC model is a challenge, but still too simple to replace clinical algorithms used by experienced physicians, which is not the same as the “clinical algorithm” defined by Takeuchi et al. Experienced physicians adjust the dose of warfarin by an individualized patient-oriented personalized method, which is an “art” and a type of “real-world practice” that is still difficult to standardize.

It is important to develop a model of “warfarin dose adjustment” that includes a consideration for the genetic variability of patients. However, it is also important to include factors other than genetic variation of warfarin-metabolizing enzymes, such as age, body size, compliance as speculated from the behavior of the patient, blood pressure control, use of drugs, patient’s preference for the drug, the patient’s favorite food, access to the hospital or clinic, economic background, previous history of various diseases, exposure to various risk factors etc, as well as the personalized genome information. In reality, both bleeding and thrombotic events in patients with atrial fibrillation in some regions of the world, such as Japan, is not as high as reported from other countries. It is important to clarify the factors that could contribute to lowering the thrombotic and bleeding risk in those regions of the world so that they can be included in the numerical modeling.

Optimal anticoagulant intervention with warfarin using computer-based modeling that takes into consideration all of...
the personal genome information, a more detailed clinical description of each patients, and clarified physician factors is awaited.

References


Figure. Mechanism of action of warfarin. Most of the warfarin absorbed into the body is bound to plasma proteins. Protein-free warfarin is metabolized mostly by CYP2C9 in the liver to form active metabolite(s). Polymorphism of CYP2C9 influences the rate of generation of the active metabolite(s) of warfarin. Functional completion of the vitamin K-dependent coagulation factor is influenced both by genetic heterogeneity of vitamin K epoxide reductase complex (VKORC) and by the local concentration of the active metabolite(s) of warfarin around that enzyme. The height and weight of the patient influence the net effect of warfarin by influencing the concentration of protein-free warfarin. The computer model includes these possible contributors.