PHARMACOGENETICS

Optimizing warfarin therapy

Almost 50% of patients on warfarin therapy are inappropriately dosed, placing them at risk of developing either life-threatening clots or serious internal bleeding. To estimate the optimal dose on an individual basis, the International Warfarin Pharmacogenetics Consortium (IWPC) has developed an algorithm that takes into consideration variation among patients in their genetic make-up and clinical profile.

At the appropriate dose, warfarin is highly effective as an anticoagulant and remains one of the most commonly prescribed drugs worldwide. However, the appropriate dose can vary considerably in different individuals, and this variability combined with a narrow therapeutic index places warfarin among the top five drugs responsible for hospitalization of patients.

The effectiveness of warfarin is influenced by several factors, including its potential to interact with other drugs—an important consideration for dosing, as patients are likely to require multiple medications. Genetic variation among individuals has also been identified as a key factor that contributes significantly to differences in responsiveness of patients. In particular, variants of two genes *VKORC1* and *CYP2C9*, which are involved in the activity and metabolism of warfarin, are known to exist in the population.

By developing a dosing algorithm that accounts for clinical and genetic variation, the initial dose of warfarin could be tailored to an individual patient. However, a reliable algorithm requires diverse data sets, representative of a global population, as shown by previous unsuccessful attempts using small populations within limited geographical regions. At a retreat hosted by the NIH Pharmacogenetics Research Network in July 2006 the idea for the warfarin consortium was initiated. After the retreat, 21 research groups from around the world joined forces, forming the IWPC. The research groups pooled their data, which is now stored and managed on the Pharmacogenomics Knowledge Base (PharmGKB). "We felt there was an opportunity to bring [together] researchers from around the world to develop a dosing algorithm on a global population," said Teri Klein, Director of PharmGKB.

With access to data from more than 5,000 patients worldwide, the IWPC developed a pharmacogenetic algorithm derived from both clinical and genetic variables. They compared dose predictions from this algorithm with those from two other models, a clinical algorithm based only on clinical data, and a fixed-dose approach. Estimates from the pharmacogenetic model were closer to the actual doses required than estimates from the other two models. "By using a combination of pharmacogenetics and clinical factors, we found that a significantly better prediction of the therapeutic dose resulted," Klein said. Currently, the IWPC is engaged in studies aimed at identifying new genetic variants that might influence the efficacy of warfarin. Prospective clinical trials are also underway in the US and Europe to compare different approaches to warfarin dosing using genetic information. The IWPC expects that their studies will help to better define the role of pharmacogenetics in optimizing warfarin therapy.

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