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Genetics determine optimal drug dose of common anticoagulant

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Genetic testing can be used to help personalize the therapeutic dosage of warfarin, a commonly-used anticoagulant, according to research published in the September 1, 2007, issue of *Blood*, the journal of the American Society of Hematology. This result represents one of the first applications of using an individual's genetic information to guide personal medical care.

Because individuals metabolize drugs differently, varying doses of warfarin are needed for the drug to be effective in each patient. Too much warfarin can cause severe bleeding, and too little can cause dangerous blood clots. Currently, there is little guidance for predicting how much of the drug a person will need. Physicians have had to roughly estimate an initial dose of warfarin and then continually monitor a patient's International Normalized Ratio (INR) value (a measure of how fast the blood clots), during treatment to tweak the dosage by trial and error.

For the first time, a group of St. Louis researchers combined the standard INR method with genetic testing to predict the therapeutic warfarin dose. Since warfarin is often prescribed after major orthopedic surgery to prevent blood clots in the legs, the study followed 92 adults undergoing either total hip or knee replacement at the Washington University Medical Center, who had never previously taken the anticoagulant.

Prior to warfarin treatment, the researchers collected blood samples and

each patient's medical history. The blood tests were used to examine variations in two genes, CYP2C9 and VKORC1, that may affect warfarin dosing. Variants in CYP2C9 impair the body's breakdown of warfarin; variants in VKORC1 cause increased warfarin sensitivity. The patients were assigned initial doses of warfarin based on clinical factors and their genotype. The researchers followed the patients until successful treatment outcomes were achieved several weeks later.

By combining variants in these genes with initial INR response and other clinical factors, the researchers derived a dosing equation that estimated the therapeutic warfarin dose. The researchers found that these two genes were important in predicting the response to warfarin. Additional factors, such as blood loss during surgery and smoking status, also correlated with therapeutic dose.

Using these data, the researchers developed a therapeutic model that could be used by physicians to refine warfarin dosage with greater accuracy than clinical factors alone. The researchers have made this dosing model publicly available on a free Web site, *www.warfarindosing.org*, and are now validating it in orthopedic and non-orthopedic patients beginning warfarin therapy.

If validated, particularly in patients taking warfarin for reasons other than orthopedic surgery, such as to prevent stroke, this gene-based dosing could predict a safe and effective warfarin dose at the start of treatment, thus minimizing the risks of the current trial-and-error approach.

Source: American Society of Hematology

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