



DNA nucleotide sequencing

PIC QUESTION OF THE WEEK: 6/09/08

Q: What is the current role of pharmacogenomics in the dosing of warfarin?

A: Warfarin is an oral anticoagulant widely used for the treatment and prevention of thromboembolic disorders. The FDA estimates that two million individuals receive prophylactic warfarin annually in the United States to prevent pulmonary emboli, heart attack, stroke, etc. Patients taking warfarin are at risk for serious adverse drug reactions, primarily those associated with hemorrhage. Other than insulin, warfarin is the most common medication responsible for hospital emergency room visits. Current practice requires close monitoring of the patient's International Normalized Ratio (INR) to avoid potentially fatal hemorrhage. It is now recognized that genetic differences may be responsible for the bleeding complications observed in some patients receiving this anticoagulant. The 2007 product labeling for warfarin reflects the newly appreciated role of pharmacogenomics in identifying an appropriate initial dose that will reduce the risk of hemorrhage. *Pharmacogenomics* is the general study of various genes that determine drug absorption, activity, distribution, metabolism, and excretion. *Pharmacogenetics* is a term that refers to the study of inherited differences in drug metabolism and response. Both terms are often used synonymously; however, the FDA appears to prefer the term *pharmacogenomics*. It has been suggested that variations in the CYP2C9 and VKORC1 genes may be responsible for nearly one-third of the cases of unexpected bleeding due to warfarin. Those patients with variants of the CYP2C9 enzyme metabolize warfarin more slowly, while those with polymorphism of the VKORC1 gene have reduced regulation of their clotting cascade. A number of manufacturers now provide test kits that can identify any alteration of these critical genes. In the past, initial doses of warfarin were determined by the general population's response to warfarin while INR levels determined subsequent dosage adjustments. INR levels are still the most effective way to monitor a patient's response to warfarin and must continue to be used; however, information on some aspects of the pharmacogenomics of warfarin could serve as a better predictor of an appropriate initial dose as well as maintenance requirements. These tests provide added cost and there are few criteria for determining which patients are the best candidates for pharmacogenomic evaluation. Regardless, this area of pharmacology will continue to generate a great deal of future study and application to drug therapy.

References:

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