Genetic information makes it safer to prescribe common blood thinner

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Doctors prescribing blood thinners have had to go through a lengthy trial-and-error process to arrive at the optimal dose for their patients. But now the process can be faster and safer, thanks to research conducted at Washington University School of Medicine in St. Louis.

Researchers there, along with colleagues at Saint Louis University and St. Louis College of Pharmacy, have developed an improved dosing formula for the widely prescribed anticoagulant warfarin (Coumadin?) that takes into account variations in two key genes. This approach is an important example of the trend toward personalized medicine.

With the new dosing formula, doctors can more quickly and accurately estimate the appropriate dose of warfarin, an anticoagulant that is notoriously challenging to use because so many factors affect its activity. Washington University investigator Brian F. Gage, M.D., medical director of Barnes-Jewish Hospital's Blood Thinner Clinic, and colleagues report their findings in the Sept. 1 issue of the journal *Blood*.

Their report follows closely upon the U.S. Food and Drug Administration's August 16, 2007 announcement of updated labeling for warfarin that includes information on the role of the two genes. At the time of the announcement, the director of the FDA's Office of Clinical Pharmacology, Larry Lesko, Ph.D., called for studies to establish proper dosing for patients with specific variations of these genes. The current study is the first to address that goal.

"We already knew these genes affected warfarin dosing, but we didn't know how to use that information clinically," says Gage, also associate professor of medicine at the School of Medicine. "But with this study, we've established a simple way to combine these genetic factors with clinical factors in a dosing algorithm."

The researchers have made the new algorithm publicly available at www.warfarindosing.org. The Web site allows physicians to input patient information and receive dosing recommendations.

Doctors prescribe warfarin to prevent blood clots or reduce the risk of stroke in patients with atrial fibrillation, artificial heart valves, deep venous thrombosis and pulmonary emboli. It is also helpful in preventing blood clot formation after certain orthopedic surgeries such as knee or hip replacements.

Until now, doctors have had to use trial and error, repeatedly changing the dose and retesting clotting time to arrive at the warfarin dose that works for each patient. During this adjustment period, which may be a matter of two to three weeks, patients are in danger of hemorrhaging when the dose is too high or blood clots and strokes when the dose is too low.

The new formula developed by Gage and colleagues calculates the proper warfarin dose using some physical and health attributes but also factors in individual variation in the two genes VKORC1 and CYP2C9. Past research showed that certain variations in these genes can affect a person's sensitivity or resistance to warfarin and how fast a person's body breaks down the drug.

The new dosing calculation better predicts each patient's response to warfarin and significantly cuts the number of dosage changes, shortening the time needed to achieve a therapeutic dose and potentially increasing

patient safety.

Gage and colleagues also adapted their approach to accommodate real-world delays in gene testing, which may take two or three days to complete. Using the new method, physicians and pharmacists can use the Web tool to estimate an initial dose based on clinical factors and once the gene tests are available, revise the initial estimate to accommodate the influence of the genetic factors.

"That approach makes our method practical," Gage says. "Physicians don't have to delay initiation of therapy while they wait for genotype results."

The dosing algorithm was established in a study of patients undergoing knee or hip replacement surgery, and Gage and colleagues are now testing it on patients with other conditions to confirm its general applicability.

Citation: Millican E, Jacobsen-Lenzini PA, Milligan PE, Grosso L, Eby C, Deych E, Grice G, Clohisy JC, Barrack RL, Burnett RSJ, Voorka D, Gatchel S, Tiemeier A, Gage BF. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood 2007 Sep 1;110(5):1511-5.

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