Medical Xpress

Genetic tests may improve dosing of widely used anti-clotting drug

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Doctors can use a patient's genetic information to more accurately prescribe doses of a commonly used blood-thinning drug whose potency and side effects vary greatly from one person to the next, reports an international team of medical scientists including researchers from the University of Florida.

Writing in the Feb. 19 issue of The *New England Journal of Medicine*, researchers describe how they developed a way to use information about a patient's genetic makeup to determine optimal doses of the anticoagulant warfarin, commonly referred to as a blood thinner.

An estimated 2 million new patients with heart conditions or other risk factors begin warfarin treatment annually in the United States, making warfarin one of the most widely prescribed drugs in the world. It is used to prevent blood clots, which can lead to heart attacks, strokes or death.

"In this study, we used data from the largest, most diverse group of patients to date to develop a method for using genetic information in combination with other patient information to determine the dosage of a very commonly used drug," said Julie A. Johnson, who directs the UF Center for Pharmacogenomics and is an associate director of the UF Genetics Institute. "This is one of the top five drugs that cause hospitalizations for adverse effects. The real value will be to patients getting warfarin therapy prescribed for the first time."

On the basis of the findings, the National Institutes of Health announced

it will soon launch the largest multicenter, randomized clinical trial in the United States to test whether a gene-based strategy for prescribing the initial warfarin dose will improve patient outcomes. The University of Florida will be one of 12 centers participating in this trial.

"Warfarin is a complicated drug to use because of its very narrow therapeutic window," said Johnson, a professor and chairwoman of UF's department of pharmacy practice. "It's a matter of balance. At one end there is a clotting risk, at the other is a bleeding risk, and in the middle is where we get the desired benefits from the drug. Finding the right dosage for a patient can be very tricky."

Adding to the challenge is that one person may need 10 times more of the drug than the next. Traditionally, doctors target the dose by taking a person's standard clinical information, such as age, weight, gender, ethnicity and health conditions, and gradually adjust the dosage over a few weeks by observing how the drug affects clotting.

However, when information about two genes, CYP2C9 and VKORC1, is factored into the initial determination, scientists found they could more accurately predict ideal dosages.

Scientists used health information and DNA samples from 4,043 patients and created three dosage procedures. One was based on age, weight and other standard health variables. A second procedure added genetic information to the patient data and was referred to as the pharmacogenetic algorithm. A third model simply used a fixed dose of 5 milligrams of warfarin per day.

After matching their predictions with what eventually turned out to be the appropriate warfarin dosage for each patient, the scientists found the pharmacogenetic method provided a significantly better prediction of the actual therapeutic dose.

The greatest benefits were observed in 46.2 percent of the patients, who required either 21 milligrams or less or 49 milligrams or more of warfarin per week, according to the study. These are the patients on the extreme ends of the dosage range who would suffer the most ill effects from an overdose.

The study included patients from countries around the world, including Taiwan, Japan, Korea, Singapore, Sweden, Israel, Brazil, the United Kingdom and the United States.

"This research study has made an important advance toward personalizing medicine — it uses data from countries around the world to develop a gene-based strategy for warfarin dosing that could benefit a wide range of patients," said Jeremy M. Berg, director of the National Institute of General Medical Sciences, or NIGMS, which partially funded the study. "This is a wonderful example of international cooperation and the results are especially valuable for the United States, since our population is so genetically diverse."

In addition to NIGMS, the National Heart, Lung and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the National Center for Research Resources supported the research.

The investigation relied on more than 20 teams in nine countries on four continents joining to form the International Warfarin Pharmacogenetics Consortium, which was spearheaded by scientists involved in the National Institutes of Health Pharmacogenetics Research Network and PharmGKB (http://www.pharmgkb.org), an online pharmacogenomics resource where data from the study is now freely available to scientists.

The clinical trial will begin in March, according to the NIH.

Source: University of Florida