THE WAR ON WARFARIN

When a Lifesaving Blood Thinner Turns Deadly, Genetics Is the Solution.

By Idelle Davidson

To explain pharmacogenomics, Dr. Lopategui refers to his mother. “My mom has always been sensitive to drug therapies. What was normal for others would always be an overdose for her. That’s because people are different genetically.” Jean Lopategui, MD, director of Molecular Pathology at Cedars-Sinai is an expert in pharmacogenomics, the study of how gene variations affect a person’s response to medications.

“We know that variations in certain genes can cause disease,” he says. “But those variations may also affect our response to medications. My mother metabolized drugs differently than my neighbor, so she needed different dosages.”

A powerful illustration is the drug warfarin (brand name: Coumadin®), one of the most popular blood thinners in the world. The drug prevents blood clots and saves lives. People with artificial heart valves or those who have experienced pulmonary embolisms, recurrent strokes, abnormal heart rhythms, or deep vein thromboses are likely taking warfarin.

And yet the drug is notoriously difficult to prescribe because of peoples’ genetic differences. So it is easy to overdose or underdose, leading the Food and Drug Administration to issue a black-box warning that strongly cautions against potentially serious side effects. Too much warfarin can increase bleeding into the gastrointestinal tract or brain, potentially leading to hemorrhage. Too little warfarin can increase the risk of blood clots and stroke. Either can be deadly. In an interesting irony, the substance started out 50 years ago as rat poison. But then researchers discovered it was also an effective and generally safe anticoagulant.

According to a 2006 report, warfarin causes some 85,000 serious bleeding events and 17,000 strokes annually. In fact, warfarin is responsible for more emergency room visits due to adverse drug reactions than any other medication, except for insulin.

But using pharmacogenomics in prescribing warfarin will likely make the drug safer, say the report’s authors, who are with the Office of Policy and Planning at the Food and Drug Administration. They conclude: “We estimate the reduced healthcare spending from integrating genetic testing into warfarin therapy to be $1.1 billion annually, with a range of about $100 million to $2 billion.”

“The numbers are staggering,” says Dr. Lopategui. “It is a very dangerous drug.” Sitting with Dr. Lopategui is Mahul B. Amin, MD, the Medical Center’s chairman of Pathology and Laboratory Medicine. Spread out before them are numerous bar charts and summaries of warfarin studies. One set, titled “Warfarin Pharmacogenomics,” illustrates the importance of relying on genetic information to determine a person’s optimal warfarin dose.

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“We did not have this knowledge until just recently,” says Dr. Lopategui, leafing through the data. “For the last 50 years, clinicians have been relying on age, height, weight, and sometimes interacting medications. It was dosing by trial and error.”

Generally, explains Dr. Lopategui, physicians start patients on 5 milligrams of warfarin. Then over several weeks they test the patient’s blood, adjusting...
the dose until it has reached a safe and therapeutic level of anticoagulation. But that waiting time may mean exposing the patient to complications from an incorrect dose.

Now scientists have the capability to determine the correct dose almost immediately with a simple blood test that looks for two genes: a warfarin-metabolizing gene and a warfarin-sensitivity gene. About 70 percent of the general population has specific variations of one of these genes. So, they will either metabolize warfarin more slowly or be more sensitive to it.

“It means that without testing, seven out of 10 patients will receive the wrong dosage,” says Dr. Lopategui. “Four out of 10 should start on a lower dose to avoid serious bleeding, and three out of 10 should start on a higher dose to avoid clotting.”

Drs. Lopategui and Amin took a leadership role in bringing the warfarin sensitivity test to Cedars-Sinai, one of the few medical centers in the U.S. to offer it. “Many physicians may not have even heard about this test,” explains Dr. Lopategui. “Others feel there is no need for it because they monitor hospital inpatients very closely and do not witness adverse events.” But outpatients are difficult to monitor as closely.

Dr. Lopategui has conducted several trials that so far have validated what he calls the “test’s predictive dosing accuracy.” For Dr. Amin, the fundamental merit of this test also lies in its function. “From the beginning,” he says, “we knew its significance in saving lives.”