Liver Success

Emerging Enzyme Test Can Predict Drug Side Effects

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Adverse drug reactions -- what most of us call side effects -- can range from annoying (headaches) to debilitating (diarrhea, vomiting) to deadly. And certain drugs -- especially psychiatric and cardiac ones -- are more apt to cause severe reactions. If only doctors had a way to predict who's most susceptible.

In many cases, they do, just by conducting a blood test or cheek swab before writing a prescription.

Researchers in the growing field of pharmacogenetics -- the study of how people's genetic make-up affects their response to medicines -- say doctors can screen for genetic variations that often prevent liver enzymes from processing certain drugs properly. When that occurs, a dose may not register at all -- or it may produce a toxic reaction. Cost for the one-time screening? Between $200 and $1,400.

David Mrazek, chairman of psychiatry and psychology at the Mayo Clinic in Rochester, Minn., says he does such testing "very regularly," especially with children (who are particularly vulnerable to drug side effects) and patients with a personal or family history of adverse drug reactions. Many other doctors in his field are unfamiliar with the tests or don't use them.

To understand how these tests work, it helps to know something about the role of both the liver and genes in drug metabolism.

The liver is responsible for regulating most chemical levels in the blood. When you swallow a pill, the medication typically travels via the bloodstream from your stomach to your liver. There, one or more types of liver enzyme process the drug, breaking it down into forms that are easier for the rest of the body to use. Some of the drug travels on through your bloodstream; the rest is tagged as poisonous and filtered out.

The most important liver enzymes in drug metabolism are the ones in the "cytochrome P450" (CYP) family. They process 25 percent of all drugs, including those that cause the most adverse reactions -- antidepressants, anti-psychotics, painkillers, beta blockers (which slow the heart rate and lower blood pressure) and drugs used to treat attention-deficit

hyperactivity disorder (ADHD).

Say you take a drug that is mostly processed by the enzyme CYP 2D6. If your liver produces too much of this enzyme, it could over-process the drug and flush it right out of your body, and you'd get no therapeutic effect. If, on the other hand, your liver produces too little of the 2D6 enzyme or none at all, the drug wouldn't be sufficiently broken down. Instead, it would build up in your bloodstream. You could overdose on what, for most people, would be a normal dose.

The Role of DNA

Just as eye color and hair color are determined by our genes, so are liver enzymes. And some vary more than others. There are more than 50 variations in the 2D6 gene. And the enzyme it governs is involved in metabolizing about 70 different drugs, including the antidepressants Paxil and Prozac and the ADHD drug Strattera, explains Mrazek. Even the popular antihistamine Claritin is metabolized by 2D6.

Like other genes, those that code for liver enzymes can vary by race and even your ancestors' geographic origin. Most people have two good copies of the 2D6 gene, so they produce a normal amount of the related liver enzyme. But an estimated 7 percent of Caucasians have two bad copies of the gene -- or no copies at all. These "poor metabolizers" don't produce any of the enzyme.

Sometimes, what you don't know can kill you. A 2000 case report in the Journal of Child and Adolescent Psychopharmacology tells of a 9-year-old boy with Tourette's syndrome, ADHD and obsessive-compulsive disorder who was treated with a combination of Ritalin, clonidine and Prozac. After 10 months on the drug regimen, he suffered seizures, then a heart attack; he later died. When an autopsy revealed toxic levels of Prozac in the child's blood and brain tissue, authorities first thought his adoptive parents had poisoned him. They were cleared when tests showed the boy was a 2D6 poor metabolizer.

Thirty percent of people who can trace their roots to North Africa and 20 percent of those whose families came from the Middle East have a different problem with 2D6: They are born with three or more copies of the gene. These "ultra-rapid metabolizers" produce too many 2D6 enzymes, which speed certain drugs out of the body. African Americans are more likely to be ultra-rapid metabolizers than whites, says Mrazek. Only 2 percent of Caucasians fall in this category.

Then there are the "intermediate metabolizers" -- those who have one good

and one bad copy of a particular gene -- say, the one for the 2D6 enzyme. Because they produce roughly half the 2D6 liver enzymes that a normal person does, explains Mrazek, they could get the same amount of a 2D6-metabolized drug into their bloodstream by taking half the normal dose. One estimate is that as many as 35 percent of Caucasians are intermediate metabolizers of 2D6.

The intermediate metabolizers are a particularly tricky group, say some experts. They might feel positive results from a drug at first, but get sick over time as it slowly builds up in their bloodstream. But because they've been on the drug for weeks or months, they might not recognize their symptoms as an adverse reaction to it.

Shirley Roberts, an African American from Orange Park, Fla., desperately wishes she'd known she was an intermediate metabolizer for both the 2D6 and the 2C19 genes. When the former parole officer suffered from severe depression in 2002, doctors first prescribed Zoloft (metabolized by the 2C19 and 2D6 enzymes, among others). The entry-level dose was okay, but when it was raised, she experienced gastrointestinal problems, hair loss, night sweats, fever and heart palpitations. She switched to Paxil (metabolized by 2D6) and then Wellbutrin (metabolized by 2D6 and three other enzymes), but bad side effects continued.

In April 2004, after nearly two years of antidepressant treatment, Roberts's doctors took her off the drugs when her blood tests showed elevated liver enzymes. Doctors first assumed she'd contracted a viral form of hepatitis, she recalls, but tests came back negative. The diagnosis: drug-induced autoimmune hepatitis, with permanent liver damage. Testing by Genelex, a DNA lab in Seattle -- at a cost of $800, paid by Roberts's insurer -- identified her enzyme problem. Roberts says she's been told her life expectancy is eight to 10 years.

So Why Not Test?

Mrazek is convinced of the value of genetic testing for enzyme problems. "Before I would put any child" on a drug metabolized by the 2D6 enzyme, he says, "I would want to know that they have at least one good copy of the 2D6 gene. . . . I've been very surprised by some very senior psychiatrists saying, 'I don't need this; I've been prescribing Prozac for years.' Young clinicians are very quick to say, 'Gee, here's a tool that can potentially prevent a tragic event.' "

But Washington psychiatrist Kelly Lynn Cozza, an assistant professor at the Uniformed Services University of the Health Sciences, regards the testing as an unnecessary expense for most patients. An alert doctor, she says, should

be able to recognize drug metabolism problems clinically. For example, she can ask patients, "Have you ever had any problems taking Robitussin? Does it make you queasy or jittery or sleepy?" Since Robitussin is metabolized by 2D6, a "yes" could be a red flag.

Cozza also notes that many factors besides DNA can affect liver enzyme production, including age, weight, diet, other drugs and smoking. Brain receptors may also affect how the body reacts to different drugs.

Then there's the question of cost. Genelex will test for a problem on one gene for $250; a battery of four tests (for genes 2D6, 2C19, 2C9 and 1A2) costs $800.

Until last year, only a few labs, like Genelex and the Mayo Clinic (whose fees are similar to Genelex's), offered this genotyping. But last year Roche Diagnostics introduced a new technology, approved by the Food and Drug Administration (FDA), that allows less specialized labs to test for genetic defects on 2D6 and 2C19. Now the labs need to convince more doctors to order the tests. Pam Sherry, a spokeswoman for Roche's LabCorp, quoted a "ballpark retail" price of $1,360 -- but said insurers that have contracts with LabCorp will probably pay less.

But many policies -- including ones from Aetna, CareFirst BlueCross BlueShield and Cigna HealthCare -- won't pay at all, because the insurers consider use of the testing in clinical practice "experimental and investigational." UnitedHealthcare doesn't have a written policy on cytochrome P450 testing yet, says spokesman Steven Matthews, but the company's plans -- including M.D.-IPA and Optimum Choice -- may approve the testing on a case-by-case basis, if it's prescribed and used properly. Federal workers are guaranteed coverage for medically necessary testing, said Office of Personnel Management spokesman Michael Orenstein, because Federal Employees Health Benefit Plan contracts stipulate that FDA-approved tests may not be considered investigational.

But do you really want your health insurance plan to pay for the testing? Cozza posed an interesting question: If your insurer learned that you had a CYP defect . . . could it decide to require preapproval for every prescription any doctor writes for you?

No insurance plans are paying for routine genotyping yet. But the field of pharmacogenetics is young. "My prediction," said Mrazek, "is that, down the line, pediatricians will do this testing during a child's infancy." But first the labs know they have some convincing to do. 7

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