Better tests for liver toxicity would mean more medicines—and safer medicines—for patients

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How many breakthrough new drugs never reach patients because tests in clinical trials suggested a high risk of liver damage when the drug actually was quite safe?

That question underpins major international research efforts to modernize tests for drug-induced liver injury, mentioned here today at the 246th National Meeting & Exposition of the American Chemical Society (ACS), the world's largest scientific society. The meeting, which features almost 7,000 reports on new discoveries in science and other topics, continues through Thursday in the Indiana Convention Center and downtown hotels.

Paul B. Watkins, M.D., who made the presentation, explained that drug-induced liver damage is a rare drug side effect, but so serious—the No. 1 cause of sudden liver failure—that it has a disproportionate impact on a drug's fate. Liver toxicity is also the No. 1 safety concern causing pharmaceutical companies to halt development of new medicines—sometimes after spending hundreds of millions of dollars on clinical trials to establish the drug's safety and effectiveness. Likewise, it is the leading reason why drugs already on the market must be restricted or banned.

"Blood tests used today in clinical trials for assessing liver safety are the same ones we've used for at least 40 years," said Watkins, referring to

tests that measure substances released into the blood when liver cells die. "The tests do indicate damage to liver cells, and everyone assumed over the years that a positive result raised a red flag about a drug's safety. We now know, however, you can have abnormalities in these tests—even pretty remarkable ones—with drugs that pose no serious threat of damaging the liver."

Watkins described research, done with colleagues at the Hamner-University of North Carolina Institute for Drug Safety Sciences, in which healthy volunteers took prescription and non-prescription medicines that have been in use for decades and have an established safety record. The volunteers then got the standard blood tests for liver damage. Those tests measure levels of two enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are released into the blood when liver cells die. The results showed alarmingly high AST/ALT levels, which the scientists first thought were false-positive results, meaning that liver cells weren't really dying. Follow-up tests, however, verified that liver cells were dying.

Those experiments led to a realization that drugs can cause liver cells to die, produce elevated AST/ALT levels in patients, but not cause the kind of permanent liver damage that can mean a liver transplant or death. In most cases, the liver recovers and adjusts, and patients actually can continue taking the medication without risking permanent damage, Watkins explained.

In other patients, Watkins suspects, the immune system goes into overdrive in response to the initial damage and mistakenly begins to attack and kill liver cells. If that's the case, a test that accurately predicts the risk of permanent liver damage would detect the proteins and genes associated with activation of the immune system.

Watkins' group and other research teams in the Drug-Induced Liver

Injury Network (DILIN), which he leads, are now on the hunt to find markers that could be better indicators of liver safety. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established DILIN to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs and alternative medicines, such as herbal products and supplements.

DILIN is among major international efforts to develop better tests for predicting serious side effects of medicines. The European Union, for instance, is seeking better tests for liver, kidney and heart damage with its SAFE-T consortium. And the Predictive Safety Testing Consortium (PSTC) helps drug companies come together to validate safety testing methods. The U.S. Food and Drug Administration and its European and Japanese counterparts—the European Medicines Agency and the Japanese Pharmaceutical and Medical Devices Agency—advise the PSTC.

Better tests would help save some drugs from being abandoned during development and might mean new life for medicines dropped on the basis of AST/ALT tests during the last 40 years, Watkins said. Dozens or more such drugs could find a new life in medicine, he said.

Improved liver toxicity tests may be a long way off. Watkins explained that development of such tests is just the first step. Then the tests must be validated on thousands of blood samples from patients with different diseases taking different drugs. Watkins is currently working to set up a liver safety consortium to get drug companies to work together and collect these samples to evaluate new tests.

More information: Abstract:

Biomarkers for the diagnosis and management of drug-induced liver injury

Genome-wide association studies (GWAS) have linked specific HLA alleles to the risk for developing DILI due to several drugs. These insights have not yet led to personalized medicine approaches to risk management of DILI because the associations lack specificity. That is, although prospective genetic testing would identify most patients susceptible to DILI, it would deny treatment to many more patients who could be safely be treated with the drug. For this and other reasons, there is intense interest in developing non-genetic biomarkers that could be useful in DILI risk management. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been used for over 40 years to monitor the liver safety of drugs and are sensitive measures of liver injury. However, there are drugs that, when administered at recommended doses, are quite safe for the liver yet cause marked elevations in serum ALT and AST. We have been exploring whether current mechanistic biomarkers can distinguish benign enzyme elevations from those that may lead to clinically important liver injury. We have analyzed serial serum samples obtained from cohorts of healthy adult volunteers treated with different therapeutic drug regimens that can cause marked elevations in serum ALT and AST but have low or no risk for serious hepatotoxicity (acetaminophen, various heparins, and cholestyramine). We and our collaborators have employed a variety of techniques, including transcriptomics, metabolomics and proteomics to identify biomarkers that may provide insight into the mechanisms underlying these benign and self-limited laboratory abnormalities. These studies indicate that recurrent therapeutic doses of acetaminophen, heparins and cholestyramine cause hepatocyte death, but the mechanisms involved in cell death differ between these treatments. The reason why these treatments are safe for the liver remains unclear but several theories will be discussed.

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