Researchers use liver-function model to solve mystery of deadly diabetes drug

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(Medical Xpress)—Using a computer model developed by the Hamner Institutes for Health Sciences, researchers at the University of North Carolina at Chapel Hill believe they have solved the mystery of why a diabetes drug introduced in 1997 caused liver failure and death in 63 patients.

Their discovery makes it likely that similar drug-related deaths can be prevented in the future.

Sixty-three deaths

In 1997, troglitazone was approved for use in the U.S. as one of the first drugs designed to treat type 2 diabetes. It was withdrawn from the market in 2000 after 63 people died from liver failure after taking it.

No one at the time really understood what happened. In preclinical studies using rats, there was no sign of danger to the liver. During human trials, adverse effects from the drug were characterized as rare and relatively mild. There were some hints at the potential for liver damage, but it wasn't enough to prevent approval by the Food and Drug Administration.

"Rats didn't have a problem handling the drug, and the human trials weren't large enough for the true risk of liver injury to become apparent," said Paul Watkins, co-author of the study and professor of

medicine and pharmacy at UNC. He is the director of the Hamner-UNC Institute for Drug Safety Sciences.

"Once the drug was given to a larger population that contained patients unable to properly process the drug, people started to turn yellow and die of liver failure."

Landmark study reveals unknown differences

The research team at the UNC Eshelman School of Pharmacy used DILIsym, a computer program designed to predict how drugs will affect the liver. The team combined information about troglitazone with data specific to the human liver generated in the lab of Kim Brouwer, Kenan Distinguished Professor at the UNC pharmacy school.

In a simulated population, the model successfully predicted that rare patients would develop life-threatening liver injury while also suggesting what factors make these patients susceptible. The team's findings were published online in Clinical Pharmacology and Therapeutics.

"The simulation we used was able to predict the effects that were seen in patients who actually took troglitazone when it was on the market," said Kyunghee Yang, lead author of the study. "In addition to this, the model was also able to describe the mechanisms that may have caused the liver damage."

The researchers cite the accumulation of bile acids, substances produced by the liver that promote digestion and aid in the absorption of fats, as the most likely suspect in the deaths.

"Bile acids are like detergents," Yang said. "If they accumulate in the liver, they can cause cell death. Increased bile acid concentrations in the liver may lead to liver damage. This is one of the possible mechanisms

we proposed."

Yang conducted her research under the guidance of Brouwer, senior author of the paper. Brouwer calls this a "landmark study."

"This is really exciting work that will change the way scientists think about how we can predict the danger of drug-induced liver injury," she said.

A model of safety

The UNC study showed that a computer model could accurately forecast the occurrence of troglitazone-induced liver injury. The model also predicted that rats respond differently to the drug than humans, a critical insight as animal testing precedes human trials.

"Before DILIsym, no one had been able to completely explain troglitazone liver injury or suggest improved approaches so drug companies could avoid similar problems in the future," Brouwer said. "It turns out that animals do a poor job predicting human drug-induced liver injury. There are lots of explanations, but one important reason is that bile acids are different in each species. Recent data suggest that the use of humanized systems has greater predictive power for adverse events like DILI."

Drug-induced liver injury is the most common reason drug-development programs are terminated. It is also the leading cause of regulatory actions that lead to failed or stalled drug approvals, market withdrawals, usage restrictions, and warnings to physicians, Watkins said.

"Rare liver toxicity is now the major safety concern with new drugs and can often be detected only after many thousands of patients have received treatment," Watkins said. "We believe that the application of

DILIsym will greatly improve drug safety while minimizing animal testing and reducing the costs of new medicines."

The DILIsym software is the result of the DILI-sim Initiative, a partnership between the Hamner-UNC Institute for Drug Safety Sciences and fourteen major drug companies that shared data to develop a tool that can predict a drug's risk of injuring the liver.

"This is a beautiful illustration of the power of computer modeling of liver injury as a predictive tool," said Neil Kaplowitz, a leading expert on effects of drugs and alcohol on the liver at the University of Southern California. "The outcome here is truly remarkable in its closeness to what actually happened in a real patient population more than twenty years ago. The results provide a strong impetus to forge ahead with this novel approach."

More information: "Systems Pharmacology Modeling Predicts Delayed Presentation and Species Differences in Bile Acid–Mediated Troglitazone Hepatotoxicity." K Yang, J L Woodhead, P B Watkins, B A Howell and K L R Brouwer. *Clinical Pharmacology & Therapeutics* (28 July 2014) | DOI: 10.1038/clpt.2014.158

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