Inflammatory clues to drug toxicity

Henry Nicholls, BMN News

Drug toxicity is bad news for livers and bad news for drug companies. However, according to one hypothesis, low-level inflammation could account for the idiosyncrasies of toxic reactions, and knowing this could increase the number of drugs that make it to the market.

Adverse reactions

The liver bears the brunt of most drug toxicity responses, and such responses, although rare, can cause a promising pharmaceutical to be dropped from development, or in some cases to be withdrawn from the market subsequent to release. But despite their significance to drug companies, these adverse reactions are still difficult to predict.

The delay between taking a drug and the onset of a toxic response is extremely variable, and the effect of drug dose on toxicity is hard to define, says Robert Roth of the Department of Pharmacology and Toxicology at Michigan State University (http://www.msu.edu).

One hypothesis that might explain this idiosyncrasy is that different people with different genetic backgrounds have differences in their ability to metabolize drugs. The classic example is genetic polymorphism among genes encoding the liver enzyme CYP450, says David Gurwitz of the Department of Human Genetics and Molecular Medicine at Tel-Aviv University in Israel (http://www.tau.ac.il).

This polymorphism, he claims, is 'responsible for the largest part of drug recalls in recent years.' Genetic testing to identify 'poor metabolizers' would avoid many cases of drug toxicity, he suggests.

Hepatotoxicity

But the explanation of drug toxicity might be even more complicated, argues Roth. 'Compounds that are known to be hepatotoxic are much more hepatotoxic in the face of a modest ongoing inflammatory response,' he said. Such inflammation might go unnoticed by the patient, but could be enough to trigger a toxic response to a drug that would normally be metabolized without difficulty.

Roth says that these minor inflammatory reactions might be caused by endotoxins released from infective bacteria or gut microflora in response to insults like alcohol consumption, liver disease, or a change of diet. The variable levels of endotoxin might continuously alter the probability that a drug or its metabolites initiate a toxic reaction in the liver, he says.

In their latest experiments, Roth and colleagues have been studying the hepatotoxicity of ranitidine, a histamine receptor antagonist used to treat gastric ulcers and acid reflux. In a rat model, the liver is normally able to metabolize ranitidine without any trouble. However, if a mild inflammatory reaction is stimulated some hours before the rat is given the drug, there is clear evidence of damage to the liver. This, says Roth, could be of huge significance to drug companies desperate to reduce the costs incurred by hepatotoxic reactions.

Past experience

Perhaps the best example of the cost of hepatotoxicity is Pfizer's experience with Rezulin (http://www.pfizer.com), a drug marketed for type 2 diabetes. Although it was hailed 'pharmacologically very effective' and subsequently licensed, it soon became clear that in some people it triggered a mild liver injury, says Roth. Worse still, 1 in 10,000 people on the drug experienced a serious hepatotoxic reaction, which often required a liver transplant and occasionally resulted in death. The drug was withdrawn from the market.

This withdrawal is likely to have cost Pfizer hundreds of millions of dollars in lost revenue, says Bert Spilker, an independent consultant to the drugs industry, and recently the Senior Vice President of Scientific and Regulatory Affairs for Pharmaceutical Research and Manufacturers of America in Washington, D.C.

On top of the lost revenue, drug withdrawal is bad for the company's image and can lead to expensive lawsuits. 'There are few issues as important to the pharmaceutical industry as hepatotoxic ones,' Spilker told *BioMedNet News* (http://news.bmn.com). The Food and Drugs Agency's Risk Management Program is a serious attempt to uncover and address hepatotoxicity before a drug reaches the market, he says.

If the inflammation hypothesis continues to gain support, Roth says that drug companies might have to pay attention. 'If the hypothesis turns out to be true in people, then it opens the possibility for drug companies to develop animal models or maybe even *in vitro* models to predict which candidate compounds to develop as drugs before the company spends all their money on trials, marketing and lawsuits,' he said.

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