Medical Xpress

Interaction between molecules key to dangerous drug reaction

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University of Florida researchers have helped identify the underlying cause of a genetically derived, potentially fatal reaction to an anti-HIV medication, and have begun creating a less dangerous form of the drug.

A genetic mutation causes the drug, called abacavir, to hang onto molecules attached to cell surfaces, prompting the immune system to go on the offensive. Disrupting that connection prevents the negative reaction.

“Now we understand how to alter the drug so that it won’t have that adverse effect,” said lead researcher David Ostrov, an associate professor in the UF College of Medicine’s department of pathology, immunology laboratory medicine. “We hope the drug variants that we are trying to generate will help many people throughout the world by being a safer alternative.”

The findings are published in the June 19 edition of the *Proceedings of the National Academy of Sciences*.

The team’s work to understand the genetically based negative reactions to abacavir and develop a safer version of the drug could potentially eliminate the risk of those reactions and change the way scientists study reactions to drugs for conditions such as cancer or other infectious diseases.

An estimated 1.2 million people in the U.S. have HIV, according to the

Centers for Disease Control and Prevention. Abacavir, sold by itself as Ziagen or in combination with other compounds as Trizivir, Epzicom or other medications, is one of numerous antiviral drugs doctors prescribe for HIV patients. It may be used by patients who cannot take preferred medications that more effectively control the amount of virus within the body.

But about 8 percent of patients experience a serious genetically based reaction to abacavir that can cause rashes, fever, respiratory and gastrointestinal problems, peeling skin, sore throat and other symptoms. The U.S. Food and Drug Administration recommends patients undergo genetic testing before taking the drug to see if they are at risk of experiencing the negative reaction.

In many parts of the world, genetic testing is not always available for those who need it. In such cases, patients sometimes take abacavir without undergoing testing, risking the dangerous reaction. A new form of abacavir that works just as well as existing versions but doesn't carry the same threat could allow patients to safely forego genetic testing.

The team of researchers from 10 institutions studied the cause of the abacavir reaction using a visualization technique called X-ray crystallography, which involves computer analysis of patterns created when X-rays are shone through crystals of the molecules being examined.

The analysis revealed that some molecules of abacavir bind to an immune system protein instead of latching onto HIV to stop it from replicating, as the drug is designed to do. This occurs only in people who possess one specific genetic variation that produces that protein. The affected gene plays a key role in helping the immune system recognize the body's own proteins and fight off those from other potentially harmful agents.

“There are more than a thousand different versions of this particular gene,” said Ostrov, who is a member of the UF Shands Cancer Center. “The drug actually contacts the part of the molecule that is specifically unique to the gene.”

This misplaced binding draws the ire of immune system cells that, in order to function, need the protein to which abacavir has attached itself. The attacker cells, called T cells, defend the body by killing cells infected with disease-causing agents. They see misplaced abacavir molecules as invaders, and launch an assault that sets off the dangerous reaction.

Through blood testing, the researchers also verified that the attacker T cells are present in the blood of patients with the genetic variation when they take abacavir, but are not usually there.

“The solution reported is an elegant one,” said Dr. Gerold Nepom, director of Benaroya Research Institute at Virginia Mason Hospital and Medical Center in Seattle. “This finding will undoubtedly lead to similar studies for other types of adverse immune drug reactions and immune-mediated diseases that might be caused by a similar mechanism.” Nepom was not involved in the study.

The X-ray method may help scientists prevent medication-related instances of conditions such as liver damage, diabetes and lupus by allowing them to identify and address molecular interactions that cause problems. It also may help them develop drugs that have fewer potential risks in the first place.

“We are purposely designing new drug variants to prevent such adverse effects,” Ostrov said.