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Research showing cardiac risk for HIV drug results in FDA warning

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A newly published study has shown that an antiviral drug commonly used to treat HIV can cause heart abnormalities in people who have a genetic mutation in the enzyme that metabolizes the medication, potentially leading to sudden cardiac death.

Studies initially performed by researchers at Purdue University's College of Pharmacy and Indiana University's School of Medicine showed the drug efavirenz might cause a form of heart arrhythmia called torsade de pointes. Based on these findings, the drug's manufacturer performed further research, which confirmed the initial findings. The U.S. Food and Drug Administration recently approved updated labeling for the drug, marketed as Sustiva by Bristol-Myers Squibb, to include a warning regarding the risk.

Specifically, the drug has been found to cause a lengthening of a beating heart's "QT interval," which is measured with electrocardiograms.

"The longer the QT interval, the greater the risk for this heart abnormality," said Brian R. Overholser, a Purdue associate professor of pharmacy practice. "Some drugs lengthen the QT interval and they are known to have this risk factor for an abnormal heart rhythm associated with sudden cardiac death."

People at the greatest risk had a genetic abnormality in cytochrome P450 enzymes, which metabolize many drugs, eliminating them from the body. One of these enzymes, called CYP2B6, is primarily responsible

for the metabolism of efavirenz.

"This means that patients with this genetic abnormality will have greater exposure to the drug, similar to taking a higher dose, and that increases the risk for adverse effects including the one that we discovered of QT lengthening," said Overholser, who is the corresponding author of a research paper appearing in October in the *Journal of Cardiovascular Electrophysiology*.

People who have two copies of the mutated gene, inheriting one each from the mother and father, are especially at risk.

"African-Americans have a higher frequency of the mutation, so they may be more prone to the adverse reaction to the drug," he said.

Still, the overall risk of suffering sudden cardiac death is low even in African-Americans, he stressed.

"We don't want to scare people away from using this drug," Overholser said. "The new warning tells us that using this drug is a risk factor and that when we prescribe the drug we need to look at the patient's other risk factors for this arrhythmia."

The studies by Purdue and IU included both laboratory research and a clinical study of 57 people.

"We focused our study on patients carrying that mutation, and we found that the QT interval exceeded the threshold set forth by the FDA," he said.

Of the 57 people included in the study, 15 possessed the single and five possessed the double gene mutation.

"We saw a graded response, so the patients who didn't have any gene mutations didn't exceed the threshold, patients with one mutation had longer QT intervals and those with the double mutation were easily above the FDA threshold," Overholser said.

The drug is a commonly used antiviral medication to treat HIV.

"It used to be part of the primary regimen for HIV and is still used frequently, especially in Africa, where availability of newer drugs is limited," he said.

More information: AHMED M. ABDELHADY et al. Efavirenz Inhibits the Human Ether-A-Go-Go Related Current (hERG) and Induces QT Interval Prolongation inAllele Carriers, *Journal of Cardiovascular Electrophysiology* (2016). DOI: 10.1111/jce.13032

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