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Antibiotic ciprofloxacin increases risk of tears and rupture in mouse aortas

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A team of researchers at Baylor College of Medicine, the Texas Heart Institute and Baylor College of Medicine's Cardiovascular Research Institute has found that ciprofloxacin, a widely prescribed antibiotic, increases the risk of tears and rupture on the main artery of the body, the aorta, in a mouse model of human aortic aneurysms and dissections (AAD), a disease that carries high risk of death from aortic rupture. The study, which is presented today at the American Heart Association Scientific Sessions 2017, provides insights into the biological mechanism underlying the antibiotic's effects on aortic tissue and suggests that the drug should be used with caution in patients with aortic dilatation.

"Previous studies have reported that use of ciprofloxacin and other antibiotics of the class of fluoroquinolones may be associated with disruption of the normal functions of connective tissue, including tendon rupture, tendonitis and retinal detachment," said first author Dr. Scott A. LeMaire, director of research in the division of cardiothoracic surgery, vice-chair for research and professor of surgery and of molecular physiology and biophysics at Baylor College of Medicine. "These observations resulted in the drugs currently having a black box warning physicians and patients of the potential deleterious side effects."

These studies suggested that other types of connective tissues also might be involved.

"A natural tissue to worry about is the aorta, a blood vessel that relies heavily on having a sound connective tissue component – called the

extracellular matrix – to maintain its integrity," LeMaire said. "Two retrospective clinical studies looked at the possible association between fluoroquinolones and cardiovascular problems. They found that patients who received fluoroquinolones had a higher risk for aneurysms (formation of balloon-like areas in the aorta that weaken the integrity of the vessel), ruptures or dissections (tears in the wall) than patients who did not receive the antibiotics. This has raised important concerns."

Although the retrospective clinical studies point at an association between fluoroquinolone antibiotics and increased risk of aortic diseases, they do not prove that the antibiotics cause the problems. To determine whether a cause-effect association exists, LeMaire and his colleagues worked with a mouse model of human ADD.

Ciprofloxacin increases risk of tears and rupture in mouse aortas

"In our study, mice with normal or moderately stressed aortas received either ciprofloxacin or placebo and after four weeks we looked at their aortas," said senior author Dr. Ying H. Shen, director of the Aortic Diseases Research Laboratory and associate professor of surgery at Baylor College of Medicine.

The results showed that normal, unstressed mice treated with ciprofloxacin did not show significant negative effects on the aorta. In mice with moderately stressed aortas that had received the placebo, 45 percent developed AAD, 24 percent developed aortic dissection and none had rupture. On the other hand, 79 percent of the mice with moderately stressed aortas that received antibiotic developed AAD, 67 percent had aortic dissection, and 15 percent had fatal rupture. These results were similar in males and females.

"Our study suggests that in this model of moderately stressed mouse aortas, ciprofloxacin exposure results in the disease progressing more rapidly and more severely, which is exactly the concern," Shen said.

The researchers then looked deeper into the effects of ciprofloxacin on mouse aortas searching for insights into the antibiotic's mechanism of action. Compared with the aortas from stressed mice treated with the placebo, the aortic tissue of stressed mice treated with the antibiotic showed more destruction and fragmentation of elastic fibers; decreased activity of LOX, a key enzyme involved in stabilizing the extracellular matrix; increased activity of MMP enzymes involved in extracellular matrix degradation; and enhanced activation of cellular pathways that lead to cell death. Separate laboratory experiments on human aortic smooth muscle cells revealed that sustained ciprofloxacin exposure reduced the expression of LOX while enhancing the expression of MMP and inducing cell death. In these experimental settings, the antibiotic is disrupting the natural processes that maintain the integrity of the extracellular matrix that is essential for normal aortic function.

"Our findings support the concerns raised by previous retrospective clinical studies and suggest that ciprofloxacin and other antibiotics of the same class should be used with caution in patients with aortic dilatation," Shen said.

"If we consider the clinical data and our experimental results that prove causation in a reliable model of AAD, I believe we have enough evidence for changing guidelines on the use of fluoroquinolone antibiotics for people who have an aneurysm or are at risk for getting an aneurysm," LeMaire said. "I am hopeful that these guidelines can be changed in short order."

Provided by Baylor College of Medicine