True, true, or unrelated? Fluoroquinolones and aortic disease

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Central Message

Do fluoroquinolone antibiotics cause aortic disease? A new study looks for a mechanistic basis and reports extracellular matrix dysregulation in aortic myofibroblasts treated with fluoroquinolones.

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Fluoroquinolones are among the most commonly prescribed antibiotics, with nearly 30 million outpatient prescriptions filled each year in the United States.[1] These drugs have a broad antimicrobial spectrum and excellent oral bioavailability, and for this reason they are widely used to treat infections, ranging from those involving bone to those involving soft tissues, respiratory tract, gastrointestinal tract, and urinary tracts. As clinicians, we are sensitive to the fact that antibiotic use must be judicious to avoid unwanted side effects, including emergence of antimicrobial resistance and *Clostridium difficile* colitis. Narrow therapeutic windows are also a familiar concept. As we gain experience with specific drug classes, however, we are often reminded that good things come at a price, and the question is whether their benefit outweighs their risk.

The relationship between fluoroquinolones and extracellular matrix dysregulation is a story in evolution. This unexpected adverse link led to a US Food and Drug Administration (FDA) black box warning in 2008 that highlights the association between fluoroquinolones and tendon disorders. The basis for the black box warning includes several population-based studies that demonstrated an increased risk of tendonitis and rupture after recent use of fluoroquinolones, as well as in vitro and animal research. The experimental studies suggest that the mechanism may be related to upregulation of matrix metalloproteinases (MMPs) by fluoroquinolones, resulting in increased collagen breakdown.

Like tendons, the aorta is rich in collagen, and the relationship between fluoroquinolones and aortic disease is still unfolding. Regulators of collagen production and breakdown are key players in aortic disease, with dysregulation leading to aneurysms and dissection. Because fluoroquinolones may directly affect the extracellular matrix, it has been hypothesized that their use may result in aortic disease. A recent Canadian population-based study[2] reported an association between fluoroquinolone use and not only tendon disorders, but also development of aortic aneurysms. In the older adult population (≥65 years), 2.1% had tendon ruptures and 1.1% had a new diagnosis of aortic aneurysm within 30 days of treatment with fluoroquinolones. When compared with similar patients receiving amoxicillin, the hazard ratio for tendon rupture was 2.40 (95% confidence interval CI 2.98-3.28) versus 1.41 (95% CI 1.46-1.66); the hazard ratio for aortic aneurysm was 2.24 (95% CI 2.53-2.93) versus 1.50 (95% CI 1.59 to 1.90). A case-controlled Taiwanese study[3] in adults at least 18 years old also found that recent use of fluoroquinolones (within the last 60 days) was associated with a greater than 2-fold increase in risk for aneurysm and dissection. The risk remained elevated at 61-365 days after fluoroquinolone use, although its absolute value was attenuated relative to recent use. Those authors[3] found that the risk of aneurysm and dissection in patients receiving fluoroquinolones was higher if they were older (>70 years), female, or received a longer course of fluoroquinolone therapy. Their findings were supported by a recent Swedish observational study[4] that reported a 66% increase in the 60-day risk of aortic aneurysm or dissection in patients prescribed a fluoroquinolone versus amoxicillin.

In this issue of the *Journal*, Guzzardi and colleagues[5] look for a mechanistic link between fluoroquinolone use and aortic disease. In their in vitro model, myofibroblasts isolated from ascending aortic aneurysm tissue are treated in culture with various clinically relevant doses of

fluoroquinolone. The authors find that fluoroquinolone exposure attenuates type I collagen expression in a dose-dependent manner. In addition, it alters the balance of MMPs to tissue inhibitors of metalloproteinases (TIMPs), favoring extracellular matrix degradation. Guzzardi and colleagues[5] propose that a safe therapeutic window for fluoroquinolone use may exist if lower doses are chosen. At the same time, they also advise that in patients at higher risk for aortic disease (for example, those with preexisting aortopathy or connective tissue disorders), fluoroquinolones should either be avoided or used with caution.

Few experimental studies have directly examined the effect of fluoroquinolones on aortic tissue, and in this way the study of Guzzardi and colleagues[5] is important. Another recent work, by Lemaire and colleagues,[6] also shows a direct link between fluoroquinolone administration and aortic aneurysm and dissection in a mouse model of aortic disease. In that model, fluoroquinolone treatment resulted in greater expression of MMPs and elastic fiber degradation in aortic tissues.

The FDA has advised that fluoroquinolones should be avoided in uncomplicated infections when safer alternative agents can be offered. This recommendation is based on consensus that strong scientific evidence exists for such toxicities as tendon disorders and peripheral neuropathy. Thus far, the FDA has not considered there to be sufficient evidence to support specific warnings regarding fluoroquinolone use and the risk of aortic disease. At present, clinicians should be aware of the existing research in this area and consider it when making therapeutic decisions for their patients.

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