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Adverse Effects of Fluoroquinolones: Where Do We Stand?

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The FDA recently issued a new warning on aortic rupture; how should this affect practice?

The fluoroquinolone class of antibiotics has been a cornerstone of antimicrobial therapy for decades. Over the past 10 years, the U.S. Food and Drug Administration (FDA) has issued several warnings about potentially disabling adverse effects with their use, beginning with tendinopathy and tendon rupture. In July 2018, the FDA strengthened its warning that fluoroquinolones can affect glucose homeostasis adversely, particularly in elderly patients and patients with diabetes who take oral hypoglycemic agents. The European Medicines Agency (EMA) has also issued warnings on disabling and potentially permanent side effects of fluoroquinolones, stating that they should not be used in situations where other options are available or where the use of antibiotics is questionable. The use of quinolones as prophylaxis in patients with recurrent urinary tract infection and in preventing traveler's diarrhea are mentioned specifically by the EMA (https://viajwat.ch/2DC3NgD).

Now, in its most recent update, the FDA has highlighted another recognized, much less common, yet more serious adverse effect of fluoroquinolones — aortic rupture and tearing. Fluoroquinolones upregulate cell matrix metalloproteinases, resulting in a reduction of collagen fibrils of types I and III collagen, which comprise the majority of collagen in both Achilles tendons and the aorta, serving as a likely mechanism for these adverse events (*J Orthop Res* 2011; 29:67). Recently published studies demonstrated similar increased risk for aortic dissection and Achilles tendon rupture with fluoroquinolones, at about 2.5- to 3-fold compared with control populations (Pasternak et al., NEJM JW Gen Med May 1 2018 and *BMJ* 2018; 360:k678; Daneman et al., *BMJ Open* 2015; 5:e010077; *JAMA Intern Med* 2015; 175:1839; *J Am Coll Cardiol* 2018; 72:1369). Collagen also serves as a critical component of the vitreous body of the eye and in maintaining retinal attachment, but whether fluoroquinolones mediate retinal detachment is controversial.

The FDA warning regarding aortic rupture states that patients at increased risk should not be prescribed fluoroquinolones unless no other treatments are available. At-risk patients identified in the warning include those with known aortic or other arterial aneurysms, hypertension, or peripheral vascular disease; the elderly; and patients with rare genetic conditions affecting collagen structure, such as Marfan and Ehlers-Danlos syndromes. Interestingly, patients on long-standing glucocorticoid therapy are at increased risk for tendon rupture yet are not mentioned in the most recent warning (*Int J Antimicrob Agents* 2010; 35:366).

The risk for aortic rupture or dissection from quinolones is approximately 1 to 2 cases per 10,000 treatment courses, according to Pasternak et al. and Daneman et al. Unfortunately, the risk for aortic rupture is not necessarily linked to prolonged duration of therapy. In the Pasternak study, 41% (26/64) of cases of aortic rupture occurred in the first 10 days of quinolone treatment and 55% had occurred within 20 days. The Daneman study showed a median of 20 days of therapy at time of rupture. Thus, the aortic rupture risk is not necessarily confined to patients on long-term therapy.

The new FDA warning clashes indirectly with Infectious Diseases Society of America community-acquired pneumonia (CAP) treatment guidelines, which suggest use of fluoroquinolones in high-risk patients with comorbid conditions and patients at risk for drug-resistant *Streptococcus pneumoniae* (*Clin Infect Dis* 2007; 44 Suppl 2:S27). These patients — who frequently are elderly and have hypertension or vascular disease — are precisely those for whom "health care professionals should avoid prescribing fluoroquinolone antibiotics," according to the FDA warning. The rates of resistance of *S. pneumoniae* to doxycycline and macrolides may be as high as 15% to 30%, whereas rates of resistance to quinolones remain at or below 1%. Therefore, if quinolones were abandoned for such patients, the number of patients receiving inadequate antimicrobial coverage would likely exceed the number of patients who would be spared aortic rupture. For example, assuming that one third of CAP cases are caused by *S. pneumoniae* and that one quarter of these cases are resistant to nonquinolone therapy, about 8% of patients with CAP would receive inadequate treatment.

Wrap-Up (Riepilogo)

Potential adverse effects — including aortic rupture and dissection — should be considered routinely in the assessment of benefits and harms associated with fluoroquinolones. For example, the benefit-harm calculus for an elderly mildly hypertensive patient with severe community-acquired pneumonia surely differs from that of a patient with a known aortic aneurysm or a collagen disorder and marginal indications for fluoroquinolone therapy. However, for patients between these extremes, the task is not straightforward. Particularly in busy settings such as emergency departments and urgent care centers, the pressure to make quick decisions about antimicrobial coverage may preclude thoughtful deliberation about relatively small risks for adverse drug effects. Nevertheless, patients should be made aware of these potential side effects when fluoroquinolones are prescribed. Additional data to better characterize the benefit-harm profile of fluoroquinolones would be desirable in the long term, but guidelines should be updated as soon as possible to advise clinicians more specifically on when to prescribe these drugs.

CITATION(S):

U.S. Food and Drug Administration. Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. December 20, 2018. (https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm)