Minimizing the Risk of Tendon Injury Associated With Fluoroquinolone Use

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Fluoroquinolones are a frequently prescribed antibiotic class in the United States, and safety concerns about these agents have gained increased attention in recent years. In 2016, the Food and Drug Administration (FDA) issued an advisory that the risk of serious adverse reactions associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options.[1]

One well-described and serious adverse event associated with fluoroquinolones is tendinitis and tendon rupture. These injuries can result in long-term sequelae, including chronic pain and mobility restrictions, and may warrant surgical intervention.[2] Due to the severity of these adverse events, a black-box warning is included in the product labeling of all fluoroquinolones in the United States. In the general population, the estimated occurrence rate of fluoroquinolone-induced tendinopathy is from 0.14% to 0.4%.[3]

CLINICAL PRESENTATION

Fluoroquinolone-induced tendinopathy most commonly involves weight-bearing tendons. Although these adverse effects have involved the Achilles tendon in the majority of cases, they have also been reported to occur in the rotator cuff, hands, wrists, biceps, thumbs, and other tendon sites.[4,5] One study suggested that nearly 90% of fluoroquinolone-induced tendon injury cases involved the Achilles tendon.[6] Achilles tendon disorders are characterized by edema, tenderness, and swelling, and they are often accompanied by sharp pain with walking.[4,7] Symptoms tend to occur acutely, and severity appears to correlate with the degree of edema.[8] Rupture is often preceded by tendinitis but may occur without forewarning.[4] Symptom onset varies considerably, and studies report an average onset of 9 to 13 days after fluoroquinolone therapy initiation (range, 1-152 days).[4,9-12] Diagnosis of tendinitis or tendon rupture is commonly based on clinical presentation and physical examination findings, although imaging studies may also be used.[6]

PROPOSED MECHANISM

Fluoroquinolones have been hypothesized to compromise tendon function and increase risk of injury, especially in weight-bearing joints most subject to mechanical force,[8] via several possible mechanisms. These medications may cause direct tissue injury, including necrosis or exposure-dependent cellular apoptosis.[13] They may also induce toxicity indirectly by stimulating local release of tissue-damaging substances, including nitric oxide and oxygen-derived species, or by stimulating enzymes that degrade collagen.[7,14,15]

Another hypothesis is that fluoroquinolones may inhibit mammalian DNA topoisomerase II, resulting in cellular mitochondrial toxicity.[8] Fluoroquinolones, which are known chelators of cations, may deplete divalent ions essential for appropriate integrin receptor signaling.[8,13]

WHO IS AT RISK?

In a database study of 6.4 million patients in the United Kingdom,[16] 28,907 cases of Achilles tendinitis and 7685 cases of Achilles tendon rupture were identified. The use of a fluoroquinolone was strongly associated with Achilles tendinopathy (odds ratio [OR], 4.3; 95% CI, 3.2-5.7) and tendon rupture (OR, 2.0; 95% CI, 1.2-3.3). The association with Achilles tendinitis was stronger among individuals who were older than 60 years, who were not obese, and who used oral glucocorticoids. The association with tendon rupture was stronger in women.

The risk of tendinopathy may be exposure-related, so doses of fluoroquinolones should be adjusted based on renal function to avoid possible drug accumulation.[3] Although tendinopathy is considered a class-wide toxicity, data analysis of animal studies and patient reports suggests that levofloxacin and its parent compound ofloxacin have a greater propensity to cause tendon damage compared with other fluoroquinolones.[2]

MANAGEMENT

The FDA recommends that at the first sign of tendon pain, swelling, or inflammation, patients should stop taking the fluoroquinolone, avoid exercise and use of the affected area, and promptly contact their health care provider for tendon evaluation and transition to a nonfluoroquinolone antibiotic. Evidence regarding the safety of continuing fluoroquinolone therapy at a decreased dose, switching to an agent in another class with possibly lower tendinopathy risk, or fluoroquinolone rechallenge after injury is limited to case reports.[6]

Tendinopathy management strategies may involve nonsurgical or surgical intervention, depending on severity. Nonsurgical strategies include the use of analgesics, physical therapy, casts,

FLUOROQUINOLONE-ASSOCIATED TENDON INJURY: KEY POINTS

- The clinical presentation most commonly involves weight-bearing tendons (Achilles tendon) and includes edema, tenderness, swelling, and sharp pain with movement.
- Symptom onset varies considerably, with an average onset of 9 to 13 days after fluoroquinolone initiation.
- Risk factors include age greater than 60 years, being nonobese, being a woman, and using oral glucocorticoids. There are more reports of adverse events with the use of levofloxacin and ofloxacin than with the use of other fluoroquinolones.
- Management consists of fluoroquinolone discontinuation and nonsurgical intervention (analgesics, physical therapy, casts, and/or immobilization) or surgical intervention, depending on severity.

and/or immobilization. Surgical intervention may be required in more severe tendon injury cases. In one review of 98 cases of tendinitis or tendon rupture, 9 patients required surgery.[6] Another analysis of only tendon rupture cases indicated that surgery was performed in 7 of 31 patients.[11]

Many patients recover from tendinopathy or rupture without debilitating consequences. In one retrospective study of 421 cases of tendinopathy, 66% of patients had a favorable recovery, usually by 15 to 30 days after therapy discontinuation.[4] However, time to recovery may be prolonged for some individuals and in rare cases may last for longer than 6 months after discontinuation of therapy.[17] Long-term complications such as swelling, pain, difficulty walking, and movement restrictions are estimated to occur in approximately 10% of cases.[4,6]

OTHER ADVERSE EFFECTS

Additional common adverse effects associated with the use of fluoroquinolones include gastrointestinal tract toxicities and, to a lesser extent, central nervous system toxicities such as peripheral neuropathy and alterations in mood. Other adverse effects include rash and other allergic reactions, QT segment prolongation, dysglycemia, hepatotoxicity, retinal detachment, and other potential connective tissue injuries such as aortic aneurysm or dissection.[9,18]

THE TAKE-HOME MESSAGE

Although the occurrence rate remains low in the general population, tendinitis and tendon rupture, in addition to other musculoskeletal toxicities, can be serious consequences of fluoroquinolone use. Clinicians should be cognizant of these adverse effects and consider other antibiotic classes for the treatment of acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections. The risks of fluoroquinolone use vs the benefits should be assessed for all other indications. Patients should also be educated about the signs and symptoms of tendon injury upon initiation of fluoroquinolone therapy. ■

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