Short overview of more serious side-effects of the fluoroquinolones

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Summary

Fluoroquinolone antibiotics have now been used since the 1980’s and are effective antimicrobials. There is now a growing body of evidence which has accumulated in the peer-reviewed literature that shows fluoroquinolones can cause pathologic lesions in tendon tissue (tendinopathy). These adverse effects can occur within hours of commencing treatment and months after discontinuing the use of these drugs. In some cases, fluoroquinolone usage can lead to complete rupture of the tendon and substantial subsequent disability. These antimicrobials are also now associated with aneurysm rapture and dissection. Time from starting the fluoroquinolone to clinical side-effect can vary from days to months making association or causality difficult.

Key Words: adverse effects, tendinitis, tendon rupture, aneurysm rapture

Introduction

The ability of fluoroquinolone antibiotics to adversely affect tendons has been the subject of many articles and case reports in the medical literature for the past 3 decades.¹

The first quinolone antibiotic, nalixidic acid which was primarily used in urinary tract infections, was introduced in the 1960s,² and this medication has undergone substantial development since then. There are now 5 generations of fluoroquinolones are effective against both gram-negative and gram-positive bacteria and can be used to treat a range of infections affecting the respiratory systems and those causing prostatitis, skin soft tissue infections, and sexually
transmitted disease. Fluoroquinolones are well absorbed when taken orally and have a long half-life; thus, dosing once or twice each day can be effective. They have been shown to be well tolerated in patients, but side effects can include gastrointestinal irritation, skin reactions, and central nervous system effects.

Serious peripheral and central nervous system effects include peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion, as well as impairment of vision, hearing, smell and taste.

Fluoroquinolones display a high affinity for connective tissue, particularly in cartilage and bone. Authors of animal studies have shown that these antibiotics may damage juvenile weight-bearing joints; therefore, these drugs are contraindicated in children. Commonly used fluoroquinolones include ciprofloxacin, levofloxacin, norfloxacin and moxifloxacin.

**Fluoroquinolone Effects Observed in Tendons**

Fluoroquinolone-associated tendinopathy was first reported in 1983. Bailey et al observed Achilles tendinopathy in a patient treated with norfloxacin for a urinary tract infection post-renal transplant. The first case of tendon rupture related to fluoroquinolones was published in 1988. Since the publication of these papers, evidence has grown in the literature regarding the tendotoxic effects of fluoroquinolones, much of which was summarized in 2 extensive reviews. Tendon pain and rupture were reported in patients treated with fluoroquinolones in a study of 98 case reports; the Achilles tendon was the principal tendon affected in 88 cases (89.8%). In an evaluation of more than 11 000 patients, rates of 2.4 incidences per 10 000 patient prescriptions for tendinitis and 1.2 per 10 000 for tendon rupture were cited. It appeared that tendinitis preceded rupture in 50% of 42 cases. Compared with the use of other antibiotics, the use of fluoroquinolones carries a 3.8-fold increased risk of Achilles tendinopathy.
Histologic Effects of Fluoroquinolones on Tendons

Normal tendon is primarily an extracellular tissue comprising mainly type I collagen fibers linearly arranged with proteoglycans and other non-collagenous proteins interspersed. The tendon cells (tenocytes) are specialized fibroblasts that produce collagen. The pathways underpinning the tendotoxic effects of fluoroquinolones are unclear, but 3 main mechanisms have been proposed: ischemia, degradation of the tendon matrix, and adverse alteration of tenocyte activity. Matrix metalloproteinases are enzymes with degrading properties that are important in the homeostasis and response to injury of tendon tissue. Fluoroquinolones facilitate expression of matrix metalloproteinases in tendon tissue; ciprofloxacin in particular has been shown to increase the expression of matrix metalloproteinase-3 in human Achilles tendon–derived cells and to reduce collagen synthesis via inhibition of tenocyte proliferation.

Clinical Presentation

The most common presenting symptom of fluoroquinolone-associated tendinopathy is pain. This pain is usually of a sudden onset and may be accompanied by acute signs of inflammation and swelling. Achilles tendon rupture may be preceded by pain, but half of tendon ruptures have been reported to occur without warning. Ultrasound and magnetic resonance imaging are both sensitive and specific for assisting in the clinical diagnosis of tendinopathy or rupture.

Speed and Latency of Onset of Tendinopathy Symptoms

In a critical review of 98 case reports of fluoroquinolone-associated tendinopathy, symptoms were reported as becoming apparent within 2 hours of taking the medication and as long as 6 months after cessation of treatment, with a median time of onset of 6 days. Eighty-five percent
of patients presented within 1 month, and 41% to 50% of patients experienced tendon symptoms after the fluoroquinolone was discontinued.14

**Affected Tendons**

The Achilles tendon is affected in most of cases of fluoroquinolone-related tendinopathy and rupture.28 Having a weight-bearing role of the Achilles tendon is thought to be the reason for the high preponderance of injury in this structure.6,29 Researchers have also reported adverse effects in a number of other tendons: the peroneus brevis,30 patellar tendon,31 adductor longus,32 rectus femoris,33 triceps brachii, finger and thumb flexor tendons, supraspinatus, subscapularis, and tendons of the hip.34

**Relative Tendon-toxicity of Fluoroquinolones**

The most tendotoxic fluoroquinolone is not known because a lack of consensus exists in the literature, but ciprofloxacin has been implicated in many case reports.28,35 In 1 patient series, pefloxacin (not used in South Africa) was responsible for most cases of fluoroquinolone-associated tendinopathy (37%), and ciprofloxacin was responsible for the second-largest percentage of cases (25.5%).14 In another series, ofloxacin was cited as the fluoroquinolone most commonly responsible for tendinopathy (38% of patients), and ciprofloxacin was the second most commonly responsible fluoroquinolone (31% of patients).16 Bartlett et al implicated pefloxacin in 68% of 421 cases.36 Levofloxacin has been cited as the least tendotoxic fluoroquinolone in humans.37 Durey et al2 showed that levofloxacin was safe and well tolerated, but authors of several case reports demonstrated Achilles tendon rupture in patients using levofloxacin37–39

**Associated Risk Factors to Fluoroquinolones’ tendotoxicity**

An independent risk of tendinopathy is associated with fluoroquinolones, but other risk factors also exacerbate this.
Data from form several *in vitro* studies have shown reduction in ultimate tensile strength of and changes in tendon ultrastructure with aging.\textsuperscript{40} The elderly have stiffer tendons and undergo adverse structural changes in the composition of the extracellular matrix in their connective tissues as part of the aging process. The age range of fluoroquinolone-related tendinopathy is broad (18 to 91 years),\textsuperscript{13} but the mean age is 59 years.\textsuperscript{14}

Low-dose corticosteroids in isolation have been implicated in Achilles tendon rupture.\textsuperscript{41} Concurrent use of corticosteroids with fluoroquinolones appears to potentiate this adverse effect.\textsuperscript{12,24,28,29} In a literature review, Khaliq co-workers reported that 21 of 40 patients (52.5%) with fluoroquinolone-related tendon rupture had received systemic or inhaled corticosteroids.\textsuperscript{14} Patients prescribed both fluoroquinolones and corticosteroids had a 46-fold greater risk of Achilles tendon rupture than those taking neither medication.\textsuperscript{42}

Fluoroquinolones undergo renal clearance; therefore, renal pathologic conditions will adversely affect their excretion and exacerbate their adverse effects.\textsuperscript{11} A further risk factor for patients with renal transplants is that they also may be prescribed corticosteroids.\textsuperscript{38}

Exercise causes a tendon response, and loading of tendons during vigorous sport participation has been cited as the principal pathologic stimulus for tendinopathy.\textsuperscript{1} Researchers found that the metabolic influence of elevated levels of adiposity also is associated with tendinopathy.\textsuperscript{43-45} Excessive loading of tendons during physical training is regarded as the main pathologic stimulus for degeneration. Exercise can increase production of matrix metalloproteinases, some of which can adversely alter the structure of the extracellular matrix of tendons.\textsuperscript{46} Several recent case reports of fluoroquinolone-associated tendinopathy have involved sporting or very physically active patients.\textsuperscript{6,24–26,34} This may be a manifestation of the combined adverse effects of tendinopathy induced by exercise and mediated by fluoroquinolones.

Lesser risk factors that are reported to exacerbate fluoroquinolone-related tendinopathy include diabetes mellitus, rheumatic disease, gout, and hyperparathyroidism.\textsuperscript{14}
Risk of aortic aneurysm and dissection

Recent studies have raised concern that fluoroquinolone antibiotics could be associated with an increased risk of aortic aneurysm. It has now also been shown that fluoroquinolones have non-antimicrobial properties that might compromise the integrity of the extracellular matrix of the vascular wall. In a nationwide propensity score matched cohort study in Sweden, there was a 66% increased rate of aortic aneurysm or dissection associated with oral fluoroquinolone use, compared with amoxicillin use, within a 60 day risk period from start of treatment. This result corresponded to an absolute difference of 82 cases of aortic aneurysm or dissection per 1 million treatment episodes; the association appeared to be largely driven by aortic aneurysm. Although the absolute risk increase was relatively small, it should be interpreted in the context of the widespread use of fluoroquinolones. These data have prompted the European Medicines Agency to initiate a safety assessment. 47-49

CONCLUSIONS

Fluoroquinolone-related tendinopathy is a complication of treatment with this family of antibiotics and usually is linked with 1 or more co-risk factors: male sex, age, renal disease, rheumatic disease, co-prescription of corticosteroid, and physical activity. If a patient who is taking fluoroquinolones presents with tendinopathy, treatment with this drug should be discontinued immediately, and an alternative, non-quinolone antibiotic should be considered. Recovery from fluoroquinolone-related tendinopathy is sometimes slower than from other types of tendinopathy and may require a less aggressive approach in the early stages of rehabilitation. Clinicians treating both athletes and the general public should be aware of the possibility of tendinopathy in patients receiving fluoroquinolone treatment, and specific questioning of patients about fluoroquinolones should form part of the subjective examination for tendinopathy. Of importance is clinicians also should be aware that fluoroquinolone-related tendon symptoms can present within hours of beginning treatment or up to 6 months after cessation.
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REFERENCES


