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Fluoroquinolones and Tendinopathy: A Guide for Athletes and Sports Clinicians and a Systematic Review of the Literature

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Context: Fluoroquinolone antibiotics have been used for several decades and are effective antimicrobials. Despite their usefulness as antibiotics, a growing body of evidence 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.

Objective: To discuss the cause, pharmacology, symptoms, and epidemiology of fluoroquinolone-associated tendinopathy and to discuss the clinical implications with respect to athletes and their subsequent physiotherapy.

Data Sources: We searched MEDLINE, Cumulative Index to Nursing and Allied Health (CINAHL), Allied and Complementary Medicine Database (AMED), and SPORTDiscus databases for available reports of fluoroquinolone-related tendinopathy (tendinitis, tendon pain, or rupture) published from 1966 to 2012. Search terms were *fluoroquinolones* or *quinolones* and *tendinopathy*, *adverse effects*, and *tendon rupture*. Included studies were written in or translated into English. Non—English–language and non-English translations of abstracts from reports were not included (n = 1).

Study Selection: Eligible studies were any available reports of fluoroquinolone-related tendinopathy (tendinitis, tendon pain, or rupture). Both animal and human histologic studies were included. Any papers not focusing on the tendon-related side effects of fluoroquinolones were excluded (n = 71).

Data Extraction: Data collected included any cases of fluoroquinolone-related tendinopathy, the particular tendon affected, type of fluoroquinolone, dosage, and concomitant risk factors. Any data outlining the adverse histologic effects of fluoroquinolones also were collected.

Data Synthesis: A total of 175 papers, including 89 case reports and 8 literature reviews, were identified.

Conclusions: Fluoroquinolone tendinopathy may not respond well to the current popular eccentric training regimes and may require an alternative, staged treatment approach. Clinicians, athletes, athletic trainers, and their medical support teams should be aware of the need to discuss and possibly discontinue these antibiotics if adverse effects arise.

Key Words: adverse effects, tendinitis, tendon rupture

Key Points

- Tendinopathy can be a complication of treatment with fluoroquinolone antibiotics and usually is linked with 1 or more synergistic factors.
- Symptoms of fluoroquinolone-related tendinopathy can present within hours of starting treatment or up to 6 months after ceasing treatment, and recovery can be slower and require a less aggressive approach early in rehabilitation than for other types of tendinopathy.
- Treatment with fluoroquinolones should be discontinued and treatment with a nonquinolone antibiotic should be considered in patients who present with tendinopathy.
- Clinicians, athletes, athletic trainers, and medical support teams should be aware of and alert to the potential adverse effects of fluoroquinolones.

The ability of fluoroquinolone antibiotics to adversely affect tendons has been the subject of many articles and case reports in the medical literature for nearly 3 decades. Clinicians, patients, athletes, and athletic trainers should be aware of the potential risks that fluoroquinolones pose with respect to both cause and potentiation of *tendinopathy*, which is described as the clinical presentation of pain associated with tendon loading.[1] These drugs also can cause tendon rupture. Therefore, the purpose of this systematic review is to discuss the cause, pharmacology, symptoms, and epidemiology of fluoroquinolone-related tendinopathy. We also discuss the clinical implications of fluoroquinolone-related tendinopathy with respect to athletes and their subsequent physiotherapy, because this type of tendinopathy requires a different rehabilitation approach to tendinopathy that is not associated with fluoroquinolones.

METHODS

Literature Search Strategy

We conducted a computerized search of the relevant scientific literature from 1966 to 2012 using MEDLINE, Cumulative Index to Nursing and Allied Health (CINAHL), Allied and Complementary Medicine Database (AMED), and SPORTDiscus. Search terms were *fluoroquinolones* or *quinolones* and *tendinopathy*, *adverse effects*, and *tendon rupture*. Included studies were written in or translated into English. Non—English–language and non-English translations of abstracts from reports were excluded.

Selection Criteria

Eligible studies were any available reports of fluoroquinolone-related tendinopathy (tendinitis, tendon pain, or rupture); animal and human histologic studies also were included. Studies were excluded if they did not focus on the tendon-related side effects of fluoroquinolones.

Included Studies

A total of 175 papers, including 89 case reports and 8 literature reviews, were identified.

Data Extraction

Data collected included any cases of fluoroquinolone-related tendinopathy, the particular tendon affected, type of fluoroquinolone, dosage, and concomitant risk factors. Any data outlining the adverse histologic effects of fluoroquinolones also were collected.

RESULTS

Fluoroquinolone Drugs and Their Side Effects

The first quinolone antibiotic, nalixidic acid, was introduced in the 1960s,[2] and this drug has undergone substantial development since then. 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.[3] Fluoroquinolones are well absorbed when taken orally[4,5] and have a long half-life; thus, dosing once or twice each day can be effective.[3,6] They have been shown to be well tolerated in patients, but side effects can include gastrointestinal irritation, skin reactions, and central nervous system effects.[7,8] 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, pefloxacin, and norfloxacin. Ciprofloxacin has been listed among the essential medications for physicians treating infections in high-level athletes[9] and has been shown to be particularly effective for treating the common problem of "traveler's diarrhea" in athletes competing abroad.[10]

Fluoroquinolone Effects Observed in Tendons

Fluoroquinolone-associated tendinopathy was first reported in 1983.[11] Bailey et al[11] observed Achilles tendinopathy in a patient treated with norfloxacin for a urinary tract infection postrenal transplant. The first case of tendon rupture related to fluoroquinolones was published[12] in 1988. Since the publication of these papers, evidence has grown in the literature regarding the tenotoxic effects of fluoroquinolones, much of which was summarized in 2 extensive reviews.[13,14] 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%).[14] 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.[15] Tendinitis preceded rupture in 50% of 42 cases.[16] Compared with the use of other antibiotics, the use of fluoroquinolones carries a 3.8-fold increased risk of Achilles tendinopathy.[17]

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 noncollagenous proteins interspersed. The tendon cells (tenocytes) are specialized fibroblasts that produce collagen.[1]

The pathways underpinning the tenotoxic effects of fluoroquinolones are unclear,[18] but 3 main mechanisms have been proposed: ischemia, degradation of the tendon matrix, and adverse alteration of tenocyte activity.[19] Matrix metalloproteinases are enzymes with degrading properties that are important in the homeostasis and response to injury of tendon tissue.[20,21] Fluoroquinolones facilitate expression of matrix metalloproteinases in tendon tissue[22]; 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.[8]

Presenting Symptoms

The most common presenting symptom of fluoroquinolone-associated tendinopathy is pain.[23] This pain is usually of a sudden onset and may be accompanied by acute signs of inflammation and swelling.[24] Achilles tendon rupture may be preceded by pain,[25,26] but half of tendon ruptures have been reported to occur without warning.[14] Ultrasound and magnetic resonance imaging are both sensitive and specific for assisting in the clinical diagnosis of tendinopathy or rupture.[27]

Speed and Latency of Onset of Tendinopathy Symptoms

In a critical review of 98 case reports of fluoroquinolone-associated tendinopathy, symptoms were reported as occurring 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]

The Effect of Dose

The concentration of fluoroquinolones in tendon tissue after standard dosing is unknown.[18] Authors of 2 studies with a combined total of 140 cases of fluoroquinolone-associated tendinopathy observed tendon symptoms at a range of daily dosages (400 to 2000 mg) with a number of different fluoroquinolones but chiefly with pefloxacin[14] and ofloxacin.[16]

Tendons Affected

The Achilles tendon is affected in 95% of cases of fluoroquinolone-related tendinopathy and rupture.[28] The 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 Tenotoxicity of Fluoroquinolones

The most tenotoxic 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 (N = 98), pefloxacin 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 (N = 42), 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[36] implicated pefloxacin in 68% of 421 cases.

Levofloxacin has been cited as the least tenotoxic fluoroquinolone in humans.[37] Durey et al[2] showed that levofloxacin was safe and well tolerated, but authors of several case reports[37–39] demonstrated Achilles tendon rupture in patients using levofloxacin.

Concomitant Risk Factors to Fluoroquinolones

An independent risk of tendinopathy is associated with fluoroquinolones, but other risk factors also exacerbate this. Authors of several in vitro studies have reported reduction in ultimate tensile strength of and changes in tendon ultrastructure with aging.[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),[13] but the mean age is 59 years.[14]

Low-dose corticosteroids in isolation have been implicated in Achilles tendon rupture.[41] Concurrent use of corticosteroids with fluoroquinolones appears to potentiate this adverse effect.[12,24,28,29] In a literature review, Khaliq and Zhanel[14] reported that 21 of 40 patients (52.5%) with fluoroquinolone-related tendon rupture had received systemic or inhaled corticosteroids. Patients prescribed both fluoroquinolones and corticosteroids had a 46-fold greater risk of Achilles tendon rupture than those taking neither medication.[42] Fluoroquinolones are cleared via the kidneys; hence, renal pathologic conditions will adversely affect their excretion and exacerbate their adverse effects.[11] A further risk factor for patients with renal transplants is that they also may be prescribed corticosteroids.[38]

Exercise causes a tendon response, and loading of tendons during vigorous sport participation has been cited as the principal pathologic stimulus for tendinopathy.[1] Researchers[43–45] found that the metabolic influence of elevated levels of adiposity also is associated with tendinopathy.

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.[46] Several recent case reports of fluoroquinolone-associated tendinopathy have involved sporting or very physically active patients.[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 (Table 1).[14]

DISCUSSION

Fluoroquinolones are effective antimicrobials but have very potent cytotoxic effects on human connective tissue.[7,51] Despite this, some clinicians still believe the risk of fluoroquinolone-related tendinopathy is negligible.[52] However, its consequences can be serious, with some patients developing substantial permanent disability.[24] Authors[26] of 1 case report attributed a death to fluoroquinolone-related tendinopathy. Athletes should not be prescribed fluoroquinolones and should be given alternative antibiotics when possible, particularly if the aforementioned risk factors are present. For example, fluoroquinolone use by athletes who require corticosteroid treatment for asthma could be hazardous. Asthma is cited as being common in sportspeople.[53]

It is generally accepted that at the first signs of fluoroquinolone-related tendinopathy, the antibiotic should be discontinued, and the patient should not be rechallenged with fluoroquinolone treatment.[2] Despite this approach becoming more widely accepted, it is not universally the case, as evidenced by at least 2 case reports of patients developing bilateral Achilles tendon rupture after being advised to persist with treatment despite the onset of tendon pain and acute signs.[24,25] However, withdrawal of fluoroquinolones after the onset of tendon pain or inflammation does not automatically ensure tendon integrity, because the tendon can become symptomatic or rupture many months after the completion of treatment. To increase awareness of fluoroquinolone tendinopathy, the US Food and Drug Administration acknowledged in 2005 the effect of fluoroquinolones on tendons and decreed that all fluoroquinolones have a black-box warning stating the risk of adverse events in tendons.[52]

Eccentric training regimes in which the tendon is subjected to sustained physiologic load have gained popularity in the treatment of tendinopathy.[54] Eccentric exercise has been reported to be successful in 90% of active or sporting individuals with tendinopathy[55] but less successful in a more sedentary population.[56] Loading a

Table 1. Risk Factors That Exacerbate Fluoroquinolone-Related Tendinopathy

Risk Factor	Age, y	Sex	Drug	Dosage	Tendon Affected	Study
Renal disease	56	Male	Norfloxacin	400 mg twice daily	Achilles	Bailey et al[11]
	77	Female	Ciprofloxacin	250 mg 4 times daily	Achilles	Damuth et al[47]
	59	Male	Ciprofloxacin	500 mg once daily	Achilles	Malaguti et al[48]
Corticosteroid use[a]	40	Female	Pefloxacin	400 mg 4 times daily	Achilles	Ribard et al[29]
	67	Male	Ofloxacin	400 mg 4 times daily	Achilles	Ribard et al[29]
	67	Male	Ciprofloxacin	750 mg twice daily	Achilles	McEwan and Davey[12]
	76	Female	Ciprofloxacin	500 mg once daily	Achilles	Lewis[24]
	62	Male	Ciprofloxacin	250 mg twice daily	Achilles	Akali and Niranjan[28]
	67	Male	Levofloxacin	500 mg once daily	Achilles	Filippucci et al[49]
Sporting or very physically active patient	41	Male	Levofloxacin	500 mg once daily	Achilles	Greene[6]
	76	Female	Ciprofloxacin	500 mg once daily	Achilles	Lewis[24]
	42	Female	Ciprofloxacin	Not stated	Hands, patella, Achilles	Ng and Naughton[25]
	91	Male	Levofloxacin	500 mg once daily	Achilles	Gottschalk and Bachman[26]
	37	Male	Ciprofloxacin	Not stated	Patella	Saint et al[31]
	63	Male	Ciprofloxacin	800 mg once daily	Rectus femoris	Karistinos and Paulos[33]
	58	Male	Levofloxacin	750 mg once daily	Hip	Ganske and Horning[34]
Diabetes mellitus	32	Male	Ciprofloxacin	500 mg twice daily	Adductor longus	Mouzopoulos et al[32]
	50	Female	Ciprofloxacin	Not stated	Achilles	Palin and Gough[50]
Rheumatic disease	81	Female	Levofloxacin	Not stated	Achilles	Vyas and Krishnaswamy[22]

[a] Parmar et al[37] reported on 4 patients with Achilles tendon rupture who were prescribed both levofloxacin and steroid therapy. No data are available about either levofloxacin or steroid dosage. The steroid was unnamed in 2 of the 4 cases.

tendon with eccentric exercise may be appropriate for treating tendinopathy in an athlete, but it may not be the best option for treating fluoroquinolone-induced tendon conditions, at least in the early stages of symptoms. In a case study, Greene[6] illustrated that patients with fluoroquinolone-related tendinopathy should be rehabilitated differently. Rehabilitation should involve a 2-phase approach consisting of a phase of bracing and support to allow the tendon to recover from the chemical injury caused by the fluoroquinolone before a second phase of progressive loading.[6]

Vitamin E has been found to protect against damage from the administration of ciprofloxacin on human fibroblast cells due to its prevention of free-radical damage in biological membranes.[7] Whether this protective effect of vitamin E can be used as a mechanism against the harmful effects of fluoroquinolones in patients is unknown.

As with the members of the nonsporting population, athletes can be susceptible to infection requiring antibiotic treatment. Guidelines have been proposed[5] for the use of fluoroquinolones in the sporting population (Table 2). These guidelines stipulate that athletes should avoid the use of fluoroquinolone antibiotics if an alternative is available. Oral or injected corticosteroids should not be administered at the same time as fluoroquinolones, athletes and their athletic trainers should be aware of the potential risks of these drugs, and close monitoring is suggested for at least 6 months after cessation of fluoroquinolone use. Athletes who are returning to participation after injury and have concomitant increased adiposity levels already will be at risk of tendinopathy[45]; hence, use of fluoroquinolones at this time may be potentially hazardous.

Table 2. Guidelines for Fluoroquinolone Use in Athletes[a]

1. Avoid the use of fluoroquinolones unless no alternative is available.
2. Oral or injectable corticosteroids should not be used concomitantly with fluoroquinolones.[b]
3. Athletes, coaches, and training staff should understand the potential risk for developing this complication.
4. Close monitoring of the athlete should be undertaken for 1 month after fluoroquinolone use.

[a] Adapted from Tsai WC, Yang YM. Fluoroquinolone-associated tendinopathy. *Chang Gung Med J*. 2011;34(5):461–467.

[b] Some evidence exists that concurrent use of inhaled corticosteroids also may be problematic.[14]

CONCLUSIONS

Fluoroquinolone-related tendinopathy is a complication of treatment with this family of antibiotics and usually is linked with 1 or more synergistic factors: male sex, age, renal disease, rheumatic disease, coprescription 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, nonquinolone 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. They also should be aware that fluoroquinolone-related tendon symptoms can present within hours of beginning treatment or up to 6 months after cessation. Clinicians, athletes, their athletic trainers, and their medical support teams should be aware of the adverse effects of fluoroquinolones.

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