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Fluoroquinolone-Associated Tendinopathy: A Critical Review of the Literature

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Abstract

With the expanded use of fluoroquinolones for the treatment of community-acquired respiratory infections and reports of tendon injury linked to the use of these agents, we reviewed the literature to investigate the frequency and strength of this association. Ninety-eight case reports were available for review. The incidence of tendon injury associated with fluoroquinolone use is low in a healthy population but increases in patients who have renal dysfunction, who are undergoing hemodialysis, or who have received renal transplants. Pefloxacin and ciprofloxacin were most frequently implicated, but tendon injury was reported with most fluoroquinolones. The median duration of fluoroquinolone treatment before the onset of tendon injury was 8 days, although symptoms occurred as early as 2 hours after the first dose and as late as 6 months after treatment was stopped. Up to one-half of patients experienced tendon rupture, and almost one-third received long-term corticosteroid therapy. Tendon injury associated with fluoroquinolone use is significant, and risk factors such as renal disease or concurrent corticosteroid use must be considered when these agents are prescribed.

The fluoroquinolone antimicrobials were first introduced in the 1980s and have since been used extensively to treat infections due to gram-negative organisms [1]. Recently, their use has expanded with the introduction of the “newer-generation” agents with improved activity against gram-positive and/or anaerobic bacteria [2]. These newer agents are now recommended for treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis [3,4]. In the Canadian guidelines for community-acquired pneumonia, fluoroquinolones used for respiratory conditions, such as gatifloxacin, levofloxacin, and moxifloxacin, are recommended as first-line therapy for patients who have received antibiotics or oral corticosteroids within the past 3 months [3]. However, reports in the literature about an association between the use of fluoroquinolones and oral corticosteroids and a possible increased incidence of tendon injuries are of concern. Therefore, a review of the literature was done to assess and describe any association found between the use of fluoroquinolones and the occurrence of tendon injury.

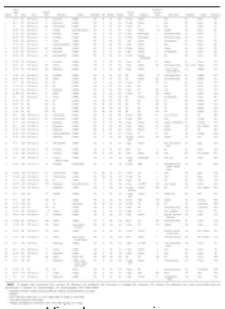
Methods

The MEDLINE database was searched for available reports of fluoroquinolone-associated tendon injury published during 1966–2001, and all appropriate reports were gathered. All references were reviewed and all English- and French-language articles were included. English translations of abstracts from reports published in other languages were also included.

Results

A total of 98 cases [5–35]. Data include the implicated fluoroquinolone, dose and duration of therapy when the tendon injury occurred, the tendon involved, time to onset of injury, the intervention(s) taken, time to recovery, and potential predisposing factors. The following text summarizes these 60 cases presented in table 1 and, when available, includes details from grouped data from case series [36–40], for a denominator of 98 cases. A comparison with the retrospective studies is presented in the discussion.

Table 1
Clinical characteristics of patients with fluoroquinolone-associated tendinopathy.



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Fluoroquinolone implicated and duration of treatment. Thirty-six (37%) of the 98 cases of fluoroquinolone-induced tendon injury were reported in association with pefloxacin. The majority of cases occurred with a pefloxacin dosage of 800 mg per day, although 1 patient reported receipt of 400 mg per day. The mean (±SD) duration of therapy was 18.2 ± 24.5 days, whereas the median duration was only 9 days. The second—most commonly implicated fluoroquinolone was ciprofloxacin (25.5% of all cases), with total daily doses ranging from 500 mg to 2000 mg, for a mean duration (±SD) of 24 ± 29.3 days (median, 7 days). Eleven cases (11.2%) were reported in association with norfloxacin (800 mg q.d.) when taken for 2–31 days total, 8 cases (8.2%) were reported in association with levofloxacin (8.2%), and 6 cases (6.1%) were reported in association with ofloxacin at 400 mg per day for 2–15 days. Five cases involving fleroxacin and 1 case involving enoxacin were also reported. Strictly speaking, enoxacin is not a fluoroquinolone, but it was included in this review.

Type of tendon injury and onset. The Achilles tendon was the most common site of injury (88 [89.8%] of 98 cases). Thirty-nine cases (44.3%) were bilateral. Other sites included the triceps epicondyle (2 cases), flexor tendon sheath (finger; 2 cases), thumb (3 cases), patellar (1 case), supraspinal tendon (1 case), quadriceps (1 case), subscapularis terrea (1 case), and rotator cuff (1 case) [6, 20,29–33, 40]. Eighty-two patients (83.7%) experienced tendinitis. The mean time of onset of symptoms (±SD) after the initiation of fluoroquinolone therapy was 17.6 ± 19.5 days; however, 50% of cases occurred within 6 days. Tendon rupture occurred in 40 subjects (40.8%), with a mean onset (±SD) of 25.6 ± 42.3 days (median, 6 days) after the initiation of fluoroquinolone treatment. Tendon injury was reported to occur as early as 2 h after receipt of the first dose of a fluoroquinolone (ciprofloxacin) [26] to as late as 6 months after treatment had been terminated [20].

Clinical aspects of tendon injury. Tendon injury manifested most commonly with pain that was severe and of sudden onset. Other frequent signs and symptoms included tenderness to palpation, edema, and difficulty with movement of the involved area [11, 27, 31, 45]. Painful nodules, thickened tendon sheaths, warmth, stiffness, and erythema were also reported. Diagnoses were made primarily by physical examination, although occasionally radiography, ultrasonography, nuclear scanning, or MRI was used.

Interventions included discontinuation of the implicated fluoroquinolone in the majority of cases, as well as nonsurgical intervention (analgesics, physical therapy, heel raise, cast, or immobilization). Surgery was described in 9 cases (table 1). In 1 case, symptoms were alleviated with a reduction in the dosage of the fluoroquinolone (norfloxacin) from 400 mg twice per day to 200 mg per day [31]. Rechallenge at the higher dosage resulted in recurrence; however, once the dosage of 200 mg per day was reinstituted, treatment was successfully continued. In another case, treatment with ciprofloxacin for 7 days resulted in improvement when instituted 2 weeks after a course of pefloxacin that was associated with tendon injury [11]. In 47 cases, treatment was not described. Recovery occurred in a mean (±SD) of 59.2 ± 101.2 days (median, 38.5 days; range, 2–600 days) with several reports describing recovery as “prolonged.” Sequelae were reported in 10 cases (10.2%) and included swelling, bruising, difficulty walking, decreased flexion, and pain.

Patient demographics and risk factors. The mean age (±SD) was 59.0 ± 16.0 years (range, 28–92 years). The ratio of men to women was 1.9 : 1. A small trend

indicated that more men experienced injury in a tendon other than the Achilles, whereas more women experienced rupture of the involved tendon. These sex differences were small and were not observed in any other outcome measurement. Thirty-two (32.7%) of 98 patients were reported to have received systemic or inhaled (minimum of 4 cases inhaled) corticosteroids before and during fluoroquinolone administration; in most cases, treatment with steroids was long-term. Twenty-one (52.5%) of the 40 patients with tendon rupture received corticosteroids. The occurrence of other risk factors that have been suggested to play a role include hemodialysis or renal dysfunction (14 cases), renal transplantation (12 cases), rheumatic disease (9 cases), gout (2 cases), diabetes mellitus (2 cases), hyperparathyroidism (3 cases), participation in sports (2 cases), and hypothyroidism (1 case).

Discussion

The results of this review suggest that male patients with a mean age of ~59 years are more likely to experience tendon injuries when receiving fluoroquinolones, although women are still susceptible, and age of affected persons had a range of 28–92 years. The preponderance of Achilles tendon injuries in boys and men has been noted in the sports medicine literature [46]. In our data set, we also noted a more frequent occurrence among men, although we found only 2 reports that involved sports-related injuries. The drugs most commonly implicated were pefloxacin and ciprofloxacin. The majority of injuries occurred in the Achilles tendon, and rupture is described in almost one-half of the reports described. Although the onset of symptoms typically occurs within 1–2 weeks, injury was also described within hours to as long as months after the initiation of treatment and even after discontinuation. Recovery took 1–2 months, requiring rest and immobilization, with a small percentage of patients undergoing surgery. Use of corticosteroids was documented for 32.7% of the patients reviewed, suggesting a possible predisposition. Another 3 patients, who were renal transplant recipients [23, 31], also likely received high-dose corticosteroid therapy.

The incidence of fluoroquinolone-induced tendon injury in an otherwise healthy population is not well established, but reports suggest that it is low, ranging from 0.14% to 0.4% [41, 43, 47]. However, a number of factors have been suggested to further predispose a patient to such injury. In the renal transplant population, an incidence of 12.2%–15.6% is reported, compared with 0.6%–3.6% for transplant recipients not receiving fluoroquinolones [44, 48]. It is possible that this is because of reduced drug clearance. It has generally been agreed that advanced age is also a predisposing factor for this injury. Other proposed factors include renal failure and/or hemodialysis, diabetes mellitus, hyperparathyroidism, rheumatic disease, gout, participation in sports, and use of corticosteroids [5, 6, 29, 31, 48]. Similar to transplant recipients, patients receiving corticosteroids appear to be predisposed to tendon injury [49]; the addition of a fluoroquinolone potentially creates additive or synergistic toxicity.

In France, Pierfitte and Royer [42] reported the largest review of patients with tendon injuries and the potential association with fluoroquinolones. Four hundred twenty-one cases were reviewed from pharmacovigilance and pharmaceutical manufacturer databases. Similar to our findings, the most commonly implicated agent was pefloxacin, to which 68% of cases were attributed. Eighteen percent of cases were attributed to ofloxacin, 8% were attributed to norfloxacin, and only 5% were attributed to ciprofloxacin; the distribution was likely a reflection of local prescribing habits. The mean duration of treatment was 13 days. Ninety-eight percent of cases occurred in the Achilles tendon. Three occurred in the rotator cuff, 2 occurred in the quadriceps femorus tendon, and 1 occurred in the biceps. Fifty percent were bilateral. The mean time to onset was earlier than in our review (9.3 days), with a similar range of 1–152 days. Recovery was reported to occur primarily in 15–30 days, although a duration of as long as 2 months was also reported, and sequelae occurred in 3%–10% of cases. This contrasts with our review, in which the mean duration of recovery was 59.2 days (median, 38.5 days). We also found that recovery could take as long 20 months, with sequelae reported in 10% of cases (table 1). The mean age was 62 years in the report by Pierfitte and Royer [42], and the ratio of male to female patients was 1.3 : 1. Risk factors were not discussed in detail, although corticosteroid use was reported for 10% of patients with tendinitis and for 30% of those with rupture [42].

Three other studies described comparisons of patients who had received fluoroquinolones with those who had not been treated in an attempt to quantify incidence and association with these agents as well as with corticosteroid therapy. A more recent retrospective study [43] reported results that were collected from an outpatient database in The Netherlands. In that study, 1841 patients who had received a fluoroquinolone were compared with 9406 patients who had received another class of antimicrobials (amoxicillin, trimethoprim, trimethoprim-sulfamethoxazole, or nitrofurantoin) to determine the association, incidence, and relative risk of using a fluoroquinolone and developing tendinopathies. Patients were excluded if they had a history of tendon injury, prior trauma, or inadequate diagnosis and if they had rheumatic disease, systemic lupus erythematosus, gout, polymyositis, Reiter syndrome, or AIDS. Of a total of 97 tendinopathies, only 22 were included: 7 that occurred with fluoroquinolone use and 15 that occurred with use of other antimicrobials during total exposure periods of 19,751 and 458,484 days, respectively. This resulted in incidences of 7.74 cases per 100,000 days for fluoroquinolones and 3.27 cases per 100,000 days for the other antimicrobials, or a relative risk of 2.4. Ofloxacin was shown to have a relative risk of 4.9. These risks adjusted to 3.7 for all fluoroquinolones and 10.1 for ofloxacin when the incidence of Achilles tendinopathies was evaluated specifically. No association was found with ciprofloxacin or norfloxacin. An association was also not found for corticosteroids.

An earlier retrospective review of 230 renal transplant recipients was done to determine whether the addition of a fluoroquinolone would increase the risk of tendinopathies in a population receiving treatment with high-dose corticosteroids [44]. Patients who underwent transplantation during the period of January 1991 through December 1992 were included. An association was defined as the occurrence of tendinopathy during or ≤15 days after discontinuation after fluoroquinolone therapy. Ninety fluoroquinolone-treated patients were compared with 140 untreated patients. No significant difference was described between the groups with respect to transplant mismatches, duration of hemodialysis, presence of diabetes, or serum creatinine levels. The fluoroquinolone group had a slightly higher mean age (50.4 vs. 46.6 years). In the treated group, 11 patients (12.2%) experienced tendinopathies, compared with 5 (3.6%) in the untreated group. Ten of the 11 treated patients received pefloxacin; 1 received its metabolite, norfloxacin. No patient who received ciprofloxacin or ofloxacin experienced tendinopathy. Of the patients who experienced tendinopathies, the fluoroquinolone-treated patients were found to have been undergoing hemodialysis for a significantly longer duration (mean duration of hemodialysis, 61.5 vs. 36.4 months). No association was found between the groups with respect to daily corticosteroid dose, duration of therapy, or number of steroid-treated acute rejections.

A brief report describing a retrospective review of renal transplant recipients supports the findings that corticosteroid dose does not affect outcome [48]. Of a total of 340 patients, 32 of whom were treated with fluoroquinolones, no difference was described with regard to duration of dialysis, degree of hyperparathyroidism, serum calcium or phosphate levels, or dose of corticosteroids. Age, however, was found to be higher for patients with tendinopathies in the treated group.

Mechanism of injury. Injuries to the Achilles tendon involving sports may be classified into various categories, varying from focal lesions to peritendonitis to rupture [50]. Pathological changes may be minimal or nonexistent in tendinitis with edema; or they may be degenerative focal disease, with granulomatous changes and capillary cell proliferation; or they may display infiltration of fibrocytes, as in chronic tendinitis [50]. Hyaline and mucoid degeneration, chondroid metaplasia of the tenocytes, and alterations in mucopolysaccharide and collagen fibers are also described. Narrowed vasculature of the tendon and paratendon suggest that changes in blood flow may play a role [46]. The low supply of blood to the tendons, particularly the Achilles, which is further decreased with age, likely predisposes to injury [46]. Degenerative changes are not thought to predispose to rupture specifically [50]. High-impact use of the Achilles tendon leads to the site being the most common for injury; however, other sites are not excluded [6].

The mechanism by which fluoroquinolones are thought to cause tendon injury has not been established, although a number of suggestions have been made. Jorgensen et al. [9] described the pathological findings for a 68-year-old man who had been treated for 3 months with pefloxacin as demonstrating degenerative lesions, fissures, interstitial edema without cellular infiltration, necrosis, and

neovascularization. Beuchard et al. [10] described a 54-year-old man who had received pefloxacin therapy for only 1 week and who had normal tendon tissue without degenerative lesions, thickening of the vasculature, hyaline deposits, and inflammatory infiltrate. It was suggested that an ischemic vascular process was the cause in these patients. Necrosis has also been noted in other patients who have received norfloxacin and ciprofloxacin [20, 28]. Le Huec et al. [6] suggested that the mechanism may be related to direct toxicity to the collagen because of the rapid onset of tendon injury [6]. In renal transplant recipients, it is possible that the reduced clearance of the fluoroquinolone results in elevated concentrations that might play a role in toxicity as the incidence increases in this population.

Animal studies. The use of pefloxacin in a mouse model demonstrated a change in proteoglycan synthesis in the Achilles tendon [51]. Oxidative damage was also found, suggesting the involvement of a reactive oxygen species. The authors proposed that age, sports activity, or corticosteroid therapy may play a role in preventing repair in the tendon. This could lead to irreversible matrix changes and rupture.

The toxic effects of various fluoroquinolones were evaluated in a juvenile rat model [52]. Edema and increased mononuclear cells were often found in the tendon sheath of the Achilles. Pefloxacin, fleroxacin, levofloxacin, and ofloxacin were found to induce the greatest number of lesions. Administration of enoxacin, norfloxacin, and ciprofloxacin had little or no effect. The authors suggested that the substituent at the seventh position of the fluoroquinolone molecule might play a role, because the agents with the highest toxicity all share a methylpiperadinyl moiety at this position, whereas the other 3 have a piperadinyl substituent. Nitric oxide and 5-lipoxygenase were also found to play a role. Another animal study described alterations in the viability of rabbit tenocytes by quinolones that are fluorinated but not by those that are not fluorinated [53]. Further studies are required to elucidate whether a structure-activity relationship exists.

In conclusion, pefloxacin and ciprofloxacin were the most frequently implicated agents, but tendon injury was reported in association with most fluoroquinolones. Overall, very few cases were from North America or continents other than Europe, which may be partly related to the fluoroquinolones implicated or available and/or to underreporting in other continents. Use of ciprofloxacin and levofloxacin is extensive in North America, and with the availability of other new fluoroquinolones, such as gatifloxacin and moxifloxacin, their use will only increase. Careful consideration should be given to the use of fluoroquinolones in combination with corticosteroids or to the use of fluoroquinolones for treating patients with renal dysfunction, because these groups are at high risk for fluoroquinolone-associated tendinopathy.

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