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ORIGINAL ARTICLE

Tendon Disorders Attributed to Fluoroquinolones: A Study on 42 Spontaneous Reports in the Period 1988 to 1998

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Objective. **Fluoroquinolone antibiotics have been associated with tendinitis and tendon rupture. In this paper we report on the followup of 42 spontaneous reports of fluoroquinolone-associated tendon disorders.**

Methods. **This study is based on cases of fluoroquinolone-associated tendon disorders reported to the Netherlands Pharmacovigilance Foundation Lareb and the Drug Safety Unit of the Inspectorate for Health Care between January 1, 1988, and January 1, 1998. By means of a mailed questionnaire, we collected information on the site of injury, onset of symptoms, treatment, and course of the tendon disorder as well as information on possible risk factors and concomitant medication.**

Results. **Of 50 mailed questionnaires, 42 (84%) were returned. The data concerned 32 patients (76%) with tendinitis and 10 patients (24%) with a tendon rupture. Sixteen cases (38%) were attributed to ofloxacin, 13 (31%) to ciprofloxacin, 8 (19%) to norfloxacin, and 5 (12%) to pefloxacin. There was a male predominance, and the median age of the patients was 68 years. Most of the reports concerned the Achilles tendon, and 24 patients (57%) had bilateral tendinitis. The latency period between the start of treatment and the appearance of the first symptoms ranged from 1 to 510 days with a median of 6 days. Most patients recovered within 2 months after cessation of therapy, but 26% had not yet recovered at followup.**

Conclusion. **These reports suggest that fluoroquinolone-associated tendon disorders are more common in patients over 60 years of age. Ofloxacin was implicated most frequently relative to the number of filled prescriptions in the Netherlands.**

KEY WORDS. Fluoroquinolones; Achilles tendon rupture; Tendinitis; Ofloxacin; Ciprofloxacin; Norfloxacin; Pefloxacin.

INTRODUCTION

Fluoroquinolones are antibacterial agents, which are commonly used because of their favorable pharmacokinetic properties, bactericidal action at low minimal inhibitory concentration, and broad antimicrobial spectrum (1,2). The most frequently observed adverse effects are gastrointestinal, followed by mild neurologic disorders (headache and dizziness) and skin reactions (2,3). Rheumatologic adverse effects are rare and consist mainly of myalgia, arthralgia, and arthritis (4). Because animal studies have shown that fluoroquinolones may damage juvenile weight-bearing joints, most fluoroquinolones are contraindicated for children and during pregnancy and lactation (4,5). Recently, fluoroquinolones have been associated with tendinitis and subsequent tendon rupture (6–15). Tendinitis

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and especially tendon rupture are serious conditions that may lead to substantial morbidity. Tendon ruptures often require surgical treatment. Risk factors most frequently associated with fluoroquinolone-induced tendon disorders include age over 60, corticosteroid therapy, and renal failure (8,9,11,13,16,17). Other well established risk factors for tendon disorders include sporting activity, a history of musculoskeletal disorders, and diabetes mellitus (18–21). The pathogenesis of fluoroquinolone-induced tendon disorders has not yet been clarified.

In this paper we report on the followup of 50 spontaneous reports of tendon disorders that were attributed to the use of fluoroquinolones, sent to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation Lareb.

PATIENTS AND METHODS

The spontaneous adverse reactions reporting scheme in the Netherlands has operated since the early 1960s. From 1988 to 1998 the former Netherlands Centre for Monitoring of Adverse Reactions to Drugs (currently, Drug Safety Unit) of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation Lareb received a total of 52 spontaneous reports of possible fluoroquinolone-induced tendon disorders. In order to obtain additional information, we sent a postal questionnaire to all health care professionals who had reported these cases. We requested additional information on the site of injury, the onset of symptoms, treatment and course of the tendon disorder, as well as the presence of possible risk factors such as a history of musculoskeletal conditions, diabetes mellitus, inflammatory bowel disease, renal failure, and sporting activities. In addition, we requested information about concomitant medication from pharmacy dispensing records.

To estimate the extent of fluoroquinolone use in the Dutch community, we used the PHARMO drug database (22). This system includes the drug-dispensing records of community pharmacies for all 300,000 inhabitants of a sample of 6 medium-sized cities in the Netherlands.

RESULTS

Between January 1, 1988, and January 1, 1998, the Drug Safety Unit of the Inspectorate for Health Care received 22 reports and the Netherlands Pharmacovigilance Foundation received 30 reports of fluoroquinolone-associated tendon disorders. Because 2 of the 52 cases were reported to both reporting centers, a total of 50 reports could be used for further analysis. The number of reports per year varied from 1.4 per 100,000 prescriptions in 1991 to 4.2 per 100,000 prescriptions in 1996.

Forty-two (84%) of the questionnaires that were sent to the health care professionals who reported these cases were returned. Thirty-two (76%) of those 42 patients had tendinitis and 10 (24%) had a tendon rupture. Sixteen cases (38%) were attributed to the use of ofloxacin, 13 (31%) to ciprofloxacin, 8 (19%) to norfloxacin, and 5 (12%) to pefloxacin. There was a male predominance (76% men, 24% women), and 71% of the patients were over 60 years of age (median 68, range 18–91). In 38 patients (90%) the reported disorder was located in the Achilles tendon. Clinical characteristics of these 38 cases are given in Table 1. In 22 patients (58%), the Achilles tendon disorder was bilateral, in 10 it was left-sided, and in 4 it was right-sided. The other tendons affected were those of the patella (quadriceps femoris) (n = 1), the epicondyles (n = 2), and the rotator cuff of the shoulder (n = 1). The following symptoms were most frequently present in the 42 reports: pain (n = 40), functional disability (n = 26), edema (n = 24), redness (n = 9), and warmth (n = 9). Most patients recovered within 2 months after cessation of fluoroquinolone therapy, but in a substantial part (n = 11; 26%) pain and disability had not recovered at followup. In 5 out of 10 cases with tendon rupture, the rupture was preceded by tendinitis. Five patients (50%) with tendon rupture underwent surgical treatment, but no histologic examination was performed. The median latency period between the start of fluoroquinolone treatment and the appearance of first symptoms was 6 days (range 1–510 days); in 93% of the cases the latency period was less than 1 month. The average duration of treatment was 14 days (range 2–81). Most patients took the fluoroquinolones according to the recommended daily dose. However, ofloxacin was taken in a dosage that was twice the recommended daily dose by 37% of the patients.

Regarding the presence of other risk factors, 11 patients (26%) had a history of joint problems and 3 (7%) had a history of trauma. Two patients (5%) had rheumatoid arthritis, 7 (17%) had osteoarthritis, 1 (2%) had gout, 2 (5%) had diabetes mellitus, 1 (2%) had psoriatic arthritis, and 1 (2%) had hyperparathyroidism. Two patients (5%) were known to have chronic renal failure but none of these patients had been treated with dialysis or had undergone renal transplantation, which are known risk factors for tendon disorders. In half of the individuals who were active in sports (n = 6), the tendon disorder occurred during sports activities. In 4 patients (10%) the blood group was known; 3 had blood group O and 1 had blood group B. Thirty-two patients (76%) had taken other drugs concomitantly with fluoroquinolones, the most frequent being anti-asthmatics (n = 14; 33%), anti-thrombotics (n = 10; 24%), H_2-receptor antagonists and proton pump inhibitors (n = 8; 19%), oral corticosteroids (n = 10; 24%), and diuretics (n = 7; 17%).

DISCUSSION

In this case series, we evaluated 42 Dutch reports of fluoroquinolone-associated tendon disorders. Overall, our case series suggests that fluoroquinolone-associated tendon disorders are more common in patients over 60 years of age. Related to the total number of prescriptions, ofloxacin was the fluoroquinolone that was implicated most frequently.

A causal relationship between the intake of fluoroquinolones and the appearance of tendon disorders is likely in the vast majority of the 42 cases. Risk factors were absent

Table 1. Characteristics of reports of Achilles tendon disorders*

Sex	Age	Drug	Dose	Indication†	TR	ADR	Localization	Outcome	Remarks/ risk factors‡
M	91	Ofloxacin	400 mg	Prostatitis	3	Achilles tendon rupture	Bilateral	Functional disability	RA, OA, RF
M	86	Ofloxacin	400 mg	COPD	17	Achilles tendon rupture	?	Recovered	DM, thoracic kyphosis
M	81	Ofloxacin	1,200 mg	?	6	Achilles tendon rupture	Bilateral	Recovered, 3 months	OA, RF
M	77	Ofloxacin	400 mg	UTI	23	Achilles tendon rupture	Left	Functional disability	
F	73	Ciprofloxacin	1,000 mg	Pyelonephritis	2	Achilles tendon rupture	Bilateral	Functional disability	Hyperparathyroidism
F	78	Ciprofloxacin	1,000 mg	URTI	13	Achilles tendon rupture	Left	Death	
F	77	Ciprofloxacin	1,000 mg	Pneumonia	16	Achilles tendon rupture	Left	Recovered, 2 months	OA
M	81	Ciprofloxacin	1,000 mg	Prostatitis	3	Achilles tendon rupture	Left	Recovered	OA
M	72	Ciprofloxacin	1,500 mg	Bronchitis	5	Achilles tendon rupture	Right	Recovered	
M	40	Norfloxacin	800 mg	UTI	6	Achilles tendon rupture	Right	Recovered	During sports
M	62	Ofloxacin	800 mg	RTI	5	Achilles tendinitis	?	Death	Bedridden
M	18	Ofloxacin	400 mg	Prostatitis	7	Achilles tendinitis	Bilateral	Recovered	Sports
M	41	Ofloxacin	400 mg	UTI	2	Achilles tendinitis	Bilateral	Persistent symptoms	Sports
M	75	Ofloxacin	400 mg	Epididymitis	7	Achilles tendinitis	Bilateral	Recovered	PAD
F	70	Ofloxacin	400 mg	RTI	3	Achilles tendinitis	Bilateral	Recovered	
M	47	Ofloxacin	200 mg	Bronchitis	21	Achilles tendinitis	Bilateral	Recovered	Psoriasis
M	79	Ofloxacin	800 mg	Bronchitis	1	Achilles tendinitis	Bilateral	Recovered, 1 week	
F	49	Ofloxacin	400 mg	RTI	20	Achilles tendinitis	Bilateral	Recovered	Thoracic kyphosis
M	72	Ofloxacin	800 mg	COPD	10	Achilles tendinitis	Bilateral	Recovered	
M	64	Ofloxacin	800 mg	Bronchitis	1	Achilles tendinitis	Right	Recovered	
M	46	Ciprofloxacin	500 mg	UTI	1	Achilles tendinitis	Bilateral	Recovered, 10 days	
M	66	Ciprofloxacin	1,000 mg	Prostatitis	150	Achilles tendinitis	Bilateral	Recovered, 2 weeks	Gout
M	68	Ciprofloxacin	500 mg	COPD	5	Achilles tendinitis	Bilateral	Recovered	
F	62	Ciprofloxacin	1,000 mg	Sinusitis	2	Achilles tendinitis	Bilateral	Recovered	
M	75	Ciprofloxacin	1,000 mg	RTI	4	Achilles tendinitis	Bilateral	Recovered	
M	45	Ciprofloxacin	750 mg	Enteritis	8	Achilles tendinitis	Left	Atrophic leg	Sports
M	75	Ciprofloxacin	1,000 mg	RTI, COPD	5	Achilles tendinitis	Bilateral	Recovered, 8 months	
M	64	Pefloxacin	800 mg	Prostatitis	4	Achilles tendinitis	Bilateral	Recovered, 3 months	
M	74	Pefloxacin	800 mg	Cath.	1	Achilles tendinitis	Bilateral	Recovered	
M	47	Pefloxacin	800 mg	Prostatitis	?	Achilles tendinitis	Bilateral	Recovered	RA, sports
M	67	Pefloxacin	800 mg	Prostatitis	25	Achilles tendinitis	Bilateral	Recovered	Obese
F	84	Norfloxacin	800 mg	UTI	4	Achilles tendinitis	Bilateral	Recovered	
M	76	Norfloxacin	800 mg	Prostatitis	13	Achilles tendinitis	Left	Recovered	DM
F	58	Norfloxacin	800 mg	UTI	5	Achilles tendinitis	Left	Recovered	
F	52	Norfloxacin	400 mg	Trigonitis	81	Achilles tendinitis	Left	Recovered	Fibromyalgia
M	70	Norfloxacin	400 mg	Prostatitis	8	Achilles tendinitis	Left	Recovered	History of tuberculous spondylitis
F	64	Norfloxacin	800 mg	UTI	7	Achilles tendinitis	Left	Recovered	
M	68	Pefloxacin	800 mg	Prostatitis	?	Achilles tendinitis	Right	Recovered, 1.5 years	OA

* TR = time relationship, in days, between first intake and tendon disorder; ADR = Achilles tendon disorder reported; ? = not reported.
† COPD = chronic obstructive pulmonary disease; UTI = urinary tract infection; RTI = respiratory tract infection; URTI = upper respiratory tract infection; Cath. = catheterization.
‡ RA = rheumatoid arthritis; OA = osteoarthritis; RF = renal failure; DM = diabetes mellitus; PAD = peripheral arterial disease.

in most patients and there was a clear temporal relationship between the first intake of fluoroquinolones and the occurrence of tendon disorders. Moreover, several similar cases have been reported in the medical literature (6–16,23–25).

It remains unclear through which mechanism fluoro-

quinolones may cause tendon disorders in humans. Because of fluoroquinolone-induced arthropathy that has been described in various juvenile animal species after high-dose administration of fluoroquinolones (4,5), most fluoroquinolones are contraindicated for children. Japanese researchers successfully produced fluoroquinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin, but not in adult rats (26). An *in vitro* study showed that the viability of rabbit tenocytes was altered by fluoroquinolones, and this effect occurred at concentrations that are comparable to therapeutic concentrations (27). The sudden onset of some tendinopathies, occasionally after a single dose of a fluoroquinolone, suggests a direct toxic effect on collagen fibers. Only a few histopathologic studies in humans have been performed. In 2 studies neovascularization, interstitial edema, and severe degenerative lesions were found, but no inflammatory cell infiltrate, which is compatible with an ischemic process (8,28). Another study showed abnormal fiber structure and arrangement, hypercellularity, and increased interfibrillar glycosaminoglycans (14). The fact that the former histopathologic findings are similar to those in overuse conditions in athletes gives credence to the premise that fluoroquinolones alter cellular function, creating an excess production of the noncollagenous extracellular matrix and a subsequent change in cell-to-matrix ratio (14).

Fluoroquinolones were associated with tendinitis for the first time in 1983 (23), and a first case of Achilles tendon rupture in a fluoroquinolone-treated patient did not appear until 1991 (29,30). Subsequently, the number of reports of fluoroquinolone-associated tendinitis with or without rupture increased (6–16,23–25), together with an expansion in the use of fluoroquinolones (31,32). Most of the reports originate from France, which may be due to publicity in that country. In the vast majority of the previously reported cases, the Achilles tendon was affected with painful tendinitis or rupture (6–8,10–13,16,23,28,33,34), but other tendons, such as the tendons of the musculus biceps brachii (35), the musculus supraspinatus (12), the musculus extensor pollicis longus (36), and the epicondyles (24), may also be affected. As in our case series, pain was the leading symptom, but edema, functional disability, and itching were also present in those case series. A finding in the literature and in our case series is that in more than 50% of the cases there was bilateral involvement of tendons (8,12,13). The latency period between start of treatment and onset of symptoms was usually 2 weeks, sometimes even a few days (8,9,12,13,16), which is consistent with our data. Duration of recovery was variable, and a substantial number of patients had persistent symptoms in the previously reported cases. In our study 26% of the patients had persistent symptoms of pain and disability that had not yet recovered at followup. Of the different fluoroquinolones, pefloxacin has been implicated most frequently, followed by ofloxacin. In our study, we had relatively few cases associated with pefloxacin, probably because of its modest market share. Tendinitis associated with other fluoroquinolones such as ciprofloxacin, norfloxacin, enoxacin, and lomefloxacin has been reported, but the incidence seems to be much lower. In our case series most of the reports concerned ofloxacin.

Risk factors most frequently associated with fluoroquinolone-induced tendon disorders include age over 60, corticosteroid therapy, and end-stage renal failure (12–14,16,37). In our study 71% of the patients were over 60 years of age, and 20% took corticosteroids concomitantly. Only 2 patients had renal failure and none of the patients had been dialysed.

Despite the relatively large volume of case-based evidence, surprisingly little is known about the epidemiology of fluoroquinolone-induced tendinitis and tendon rupture. Epidemiologic evidence is limited to one cohort study that showed that the risk of Achilles tendinitis with fluoroquinolones, especially ofloxacin, is higher than the risk with other antibacterial drugs (38). In this study the incidence rate of tendinitis with fluoroquinolones was 2.9 per 1,000 prescriptions. On the other hand, no cases of Achilles tendon rupture were found in 2,122 ciprofloxacin-treated patients (39). With prescription–event monitoring, a frequency rate of 2.4 per 10,000 patients was found for tendinitis, and 1.2 per 10,000 for tendon rupture (40). In our study the estimated frequency of tendon disorders among fluoroquinolone users was 4 per 100,000 prescriptions, which suggests that underreporting is substantial. In a study done with data from the French spontaneous reporting system, the estimated frequency of tendon disorders among fluoroquinolone users was 20 per 100,000 prescriptions (12).

In conclusion, in this study we reported on 42 cases of tendinitis or tendon rupture after fluoroquinolone therapy. Despite numerous case reports on fluoroquinolone-induced tendinitis or tendon rupture, quantitative information on this subject is scant. Physicians who prescribe a fluoroquinolone should seriously consider stopping or changing therapy at the first sign of this reaction, given the potential for severe disability.

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