Fluoroquinolone-Associated Tendinopathy of the Hand and Wrist: A Systematic Review and Case Report

HAND
2017, Vol. 12(5) NP121–NP126
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1558944717701237
hand.sagepub.com

Israel Berger^{1,2}, Isak Goodwin¹, and Gregory M. Buncke¹

Abstract

Background: Fluoroquinolone use has been known to be associated with tendinopathy and tendon rupture for over 30 years. Hand and wrist involvement has been reported rarely, yet without early recognition and withdrawal of the fluoroquinolone, there is potential for significant morbidity. **Methods:** We searched Medline using a comprehensive search strategy for fluoroquinolones and tendinopathy of the hand and wrist, and provide a case report of a possible levofloxacin-related tendon rupture in a patient with a previous mutilating hand injury. **Results:** We located 10 previously reported cases of fluoroquinolone-associated tendinopathy in the hand or wrist ranging from 1983 to 2015. Unlike Achilles tendinopathy, women were no more likely than men to have tendon rupture affecting the hands or wrists. Our patient was a 59-year-old man with prior tendon repair but otherwise noncontributory medical history who experienced spontaneous tendon rupture on an extended course of levofloxacin and required extensive pulley and boutonnière repair. **Conclusions:** Given the extensive damage that may be caused to weakened tissue, clinicians should maintain a high index of suspicion of tendinopathy in patients taking fluoroquinolones who have had previous tendon repairs, particularly in the setting of unexplained changes in recovery trajectory.

Keywords: fluoroquinolone, tendinopathy, tendon rupture, pulley reconstruction, tenolysis, tendon repair, adverse events

Fluoroquinolone use has been known to be associated with tendinopathy and tendon rupture for over 30 years.^{4,21} Fluoroquinolones such as levofloxacin and ciprofloxacin are broad-spectrum antibiotics and are commonly used in respiratory, urological, and skin infections, although fluoroquinolones can no longer be used empirically for suspected methicillin-resistant *Staphylococcus aureus* (MRSA) due to resistance.^{1,4,9,12,15} Fluoroquinolones and other broad-spectrum antibiotics are also commonly prescribed for hand and joint infections due to the need for immediate and decisive treatment of these infections to prevent bone and joint destruction.⁸ Fluoroquinolones are then continued used for known gram-negative osteomyelitis.⁸ Although fluoroquinolones are generally well tolerated and relatively safe, the side effect can be troublesome and debilitating beyond that of the original infection or suspected infection being treated. As a result of the risk of tendinopathy and other serious side effects such as peripheral neuropathy and worsening myasthenia gravis, the Food and Drug Administration (FDA) has recently recommended restricting fluoroquinolone use to complicated infections and patients for whom there is no suitable alternative antibiotic.⁷

Tendinopathy associated with fluoroquinolone use has been very well described in relation to the Achilles tendon and has an incidence of 0.08% to 2%.²⁰ Patients who are over 60 years old, nonobese, or are on glucocorticoids are at increased risk of Achilles tendinitis, while women are more likely to experience Achilles tendon rupture.^{11,23} Fluoroquinolone-associated tendinopathy affecting structures of the hand and wrist has been less frequently described, yet the small size of tendons in the hand and wrist and their proximity to adjacent structures create a point of vulnerability should severe disease occur. To assess the number of described cases, their severity, treatments, and sequelae, we conducted a systematic review of

¹The Buncke Clinic, San Francisco, CA, USA

²University of Sydney, Australia

Supplemental material is available in the online version of the article.

Corresponding Author:

Israel Berger, Centre for Values, Ethics and the Law in Medicine, Medical Foundation Building, University of Sydney, Parramatta Road, Camperdown, Sydney, New South Wales 2006, Australia.
Email: israel.berger@sydney.edu.au

Table 1. Published Cases of Fluoroquinolone-Associated Tendinopathy in the Hands.

Reference	Age/ gender	FQ/dose	Reason for FQ	Duration of FQ therapy	Onset since start of FQ	Other risk factors	Tendons	Bilateral	Tendonitis	Rupture	Diagnosis	Intervention	Sequelae
Bailey et al ³	34M	Norfloxacin 400 mg bd po 1st 3 courses, 400 mg/d po 4th & 6th courses, 800 mg/d po 5th course.	UTI	7 d, (2 wk later) 4 d, (8 wk later) 9 d, 5 d, 13 d, 4 d (31 d)	During 3 1-d course	Renal transplant on long-term glucocorticoids	Flexor tendon sheath of both middle fingers	Y	Y	N	Clinical	Dc FQ	—
Chaslerie et al ⁵	67M	Norfloxacin 800 mg/d	UTI	—	4 d	None	Left extensor pollicis longus	N	Ischemia and necrosis	Y	Clinical, surgical pathology	Surgical debridement and repair of tendon	—
DeWolf and Warhold ⁶	81M	Ciprofloxacin, — po	Ear infection	—	<7 d	None	Right extensor digitorum communis	N	N	Y	Clinical	Tendon repair	Ring MCP 18° extension lag, distance from tip of digit to distal palmar crease = 1 cm
Gillet et al ¹⁰	40F	Norfloxacin 400 mg bd po	Renal transplant, then UTI 4 mo later	8 d (D8-18 of transplant); restarted in month 5 for UTI	7 d	Renal transplant, methylprednisolone D0-D9 of transplant and prednisolone from D10	Pain in R radial styloid suggestive of de Quervain disease; tenosynovitis involving the first dorsal compartment of the wrist = extensor pollicis brevis and/or abductor pollicis longus	N	Y	N	Clinical	Dc FQ Antibrachial-palmar cast for 4 wk, and the pain gradually subsided. In the fifth month, the urinary tract infection recurred, and treatment with norfloxacin was resumed. The pain began abruptly again and occurred at the same site at the right wrist. Fluoroquinolone cessation and restoration of the cast again produced a favorable clinical outcome, this time within 2 wk.	Full recovery between episodes, no long-term follow-up reported
Lara et al ¹⁴	67F	Ciprofloxacin 250 mg bd po	Antibiotic- associated diarrhea	12 d	12 d	D22 post-AKI due to <i>Escherichia</i> <i>coli</i> -induced pyelonephritis	Flexor tendons of 2, 3, 4; extensor tendons at ICPs	N	Y	N	Serology and radiography negative	Dc FQ	None

(continued)

Table 1. (continued)

Reference	Age/ gender	FQ/dose	Reason for FQ	Duration of FQ therapy	Onset since start of FQ	Other risk factors	Tendons	Bilateral	Tendonitis	Rupture	Diagnosis	Intervention	Sequelae
Levadoux et al ¹⁶	68F	Pefloxacin	Recurrent UTI	2 d	2 d	Previous long-term use of norfloxacin and pefloxacin (over 100 tablets in 3 years)	Partial tear of third extensor tendon	N	N	Y	Clinical	Dc FQ Tendon graft from palmaris longus, sutured extensor digitorum tendons together for lateral support; hand therapy	"Slow" recovery, function returned after 2 years, remains unable to reach last degrees of extension
Liang et al ¹⁷	77F	Ciprofloxacin, — po	LUTS, empirically treated for UTI	3 d	3 d	None	Bilateral hand pain and swelling, carpal tunnel syndrome	Y	Y	N	Clinical, nerve conduction studies	Dc FQ po steroids, antihistamines, bilateral carpal tunnel releases	None after carpal tunnel releases
Rivero et al ¹⁸	49F	Levofloxacin 500 mg/d	Suspected orthopedic implant infection	90 d, (18 d later) 92 d, (57 d later) 7 d	D28 of 2nd course, D7 of 3rd course	None	Inflammation in the R 1st MCP, polyarthralgia	Bilateral polyarthralgia, unilateral inflammation	Y	N	Negative serology	Dc FQ	—
Schwald and Debray- Meignan ¹⁹	53F	Ofloxacin	Tonsillitis	8 d	22 d	Long-term glucocorticoid, physical exertion during travel	Pain in wrists and tender on palpation with no synovitis, tendinitis in L extensor forefinger, de Quervain tenosynovitis in R	Y	Y	N	Clinical	Acetaminophen, opioid, muscle relaxant (which was stopped due to GI side effects), thyroxine replacement	—
Turker and Kutz ²²	71M	Levofloxacin/500 mg bd po	Skin infection	5 d	12 d	None	Left small finger flexor digitorum profundus rupture.	N	N	Y	Clinical	Tendon repair recommended, patient refused treatment	Inability to flex left #1 DIP

Note. FQ = fluoroquinolone; M = male; d = days; Y = yes; N = no; Dc = discontinued; — = no information; F = female; D = on day (of treatment); R = right; L = left; GI = gastrointestinal; UTI = urinary tract infection; MCP = metacarpophalangeal joint; AKI = acute kidney injury; ICP = intercarpalphalangeal; LUTS = lower urinary tract symptoms; DIP = distal interphalangeal joint.

published cases of hand and wrist tendinopathy following fluoroquinolone administration. We then report a possible case of levofloxacin-associated spontaneous tendon rupture involving several tendons in the hand which required extensive surgical intervention.

Materials and Methods

We searched Medline using a comprehensive search strategy (Online Appendix A) for fluoroquinolones and tendinopathy of the hand and wrist. This provided 16 results. Abstracts were reviewed for inclusion, and 7 articles were found to relate to fluoroquinolone-associated tendinopathy in humans. No hand and wrist-specific cohort studies, cross-sectional studies, or randomized controlled trials were located. We proceeded to search reference lists forward and backward to compile a complete record of published case reports of fluoroquinolone-associated tendinopathy of the hand or wrist, which resulted in a final collection of 10 articles reporting 10 separate cases. We coded cases according to antecedent therapy factors, patient factors, tendinopathy characteristics, and treatment (Table 1).

Results

We located 10 previously reported cases of fluoroquinolone-associated tendinopathy in the hand or wrist ranging from 1983 to 2015. Patients ranged in age from 34 to 81 years (Mdn = 67) and were predominately women (60%). A variety of fluoroquinolones were associated with reported cases, including norfloxacin (3), ciprofloxacin (3), levofloxacin (2), pefloxacin (1), and ofloxacin (1), and treatment was for both suspected and proven infections. Onset of tendinopathy ranged from day 2 to 28 of treatment, while 1 patient was given levofloxacin a second time after developing tendinopathy and developed tendinitis much quicker on this course (day 7 rather than day 28). Half of patients (50%) had no known risk factors for fluoroquinolone-associated tendinopathy, while others had established glucocorticoid treatment (4), were renal transplant recipients (2), had impaired renal function (1), or had previous long-term fluoroquinolone treatment (1). Most cases were unilateral (60%) and had tendinitis (70%). A minority of cases had tendon rupture (40%), only one of which had tendinitis, in the form of ischemia and necrosis. Diagnosis was primarily clinical, and treatment in most cases entailed ceasing the fluoroquinolone and symptom relief. Surgery was recommended in all cases of tendon rupture, and bilateral carpal tunnel release was necessary in 1 tendinitis case. Long-term follow-up was uncommonly reported, but of those cases in which it was reported, outcomes ranged from full recovery to ongoing extension lag or inability to flex the affected digit. Full details of our final collection can be found in Table 1 and a summary of characteristics in Table 2. Unlike

Table 2. Summary Characteristics of Previously Published Cases of Fluoroquinolone-Associated Tendinopathy in the Hands.

Characteristic	n(%)
Patient demographics	
Age (years)	34-81 (Mdn = 67)
Female	6 (60%)
Drug characteristics	
Fluoroquinolone	
Norfloxacin	3 (30%)
Ciprofloxacin	3 (30%)
Levofloxacin	2 (20%)
Ofloxacin	1 (10%)
Pefloxacin	1 (10%)
Onset since start of last course (days)	2-28 (Mdn = 7)
On glucocorticoids	3 (30%)
Long-term use of FQ (previous or course > 21 d)	4 (40%)
Extent of disease	
Tendons affected	
Flexor digitorum	3 (30%)
Extensor digitorum	3 (30%)
Extensor pollicis brevis	1 (10%)
Extensor pollicis longus	1 (10%)
Abductor pollicis longus	1 (10%)
Carpal tunnel/carpal ligaments	2 (20%)
Joint capsule	1 (10%)
Bilateral	4 (40%)
Tendinitis	7 (70%)
Tendon rupture	4 (40%)

Note. FQ = fluoroquinolone.

Achilles tendon rupture, in this sample, there does not appear to be an increased likelihood for women to present with tendon rupture.

Case Report

A 59-year-old man presented between August and October 2015 with multiple pulley ruptures and contractures to the left index, middle, and ring fingers following a course of levofloxacin. Our patient had sustained a saw injury to the hand in December 2014 resulting in revascularization and repair to all flexor tendons in his left index, middle, and ring fingers, extensor tendon in the ring finger, and flexor pollicis longus. He underwent proximal interphalangeal (PIP) arthroplasty to the ring finger in April 2015, and after regaining excellent passive movement, in June 2015, he underwent flexor tenolysis of his index, middle, and ring fingers, as well as left ring finger A4 pulley reconstruction with sublimis tendon. He suffered a flexor tendon rupture postoperatively requiring placement of a 5-cm sublimis tendon graft 10 days later. Some ring finger erythema was noted intraoperatively, and cultures grew gram-negative

rods. A 6-week (42 days) course of oral levofloxacin was recommended at this time by an infectious disease specialist.

On day 11 of levofloxacin treatment, our patient had improved range of motion in the surgically involved fingers and was judged to be recovering well. The levofloxacin course was continued based on the recommendation of an infectious diseases specialist. On approximately day 28 of levofloxacin treatment, the patient sustained a spontaneous A2 pulley rupture to the left middle finger. He did not report the injury until day 40 of levofloxacin treatment, at which point a pulley ring splint was fitted. Our patient developed contractures over the next 2 months: a boutonnière deformity with flexion contractures of the PIP joints of the index, middle, and ring fingers, as well as extensor deformities of the distal interphalangeal joints of the middle and ring finger. Contracture release and pulley reconstruction were subsequently performed.

Our patient's medical history was otherwise noncontributory. He has no history of kidney disease, diabetes mellitus, or systemic glucocorticoid use, nor is he of advanced age. His only regular medications were fish oil and an over-the-counter multivitamin. We believe that the mutilating hand injury from which he was recovering increased his vulnerability to fluoroquinolone-related tendon rupture, resulting in spontaneous A2 pulley rupture and subsequent contractures that were unexpected given his trajectory.

Discussion

Of the published cases of fluoroquinolone-associated tendinopathy affecting the hands or wrists, women were not more likely to have tendon rupture. This contradicts previous data on Achilles tendinopathy, which have shown women to be significantly more likely to experience tendon rupture than men.^{11,23} Although few cases of hand and wrist tendinopathy have been published, this inconsistency suggests that location and severity of tendinopathy associated with fluoroquinolone use may have complex antecedents that have yet to be identified.

It is also worth noting that many of the hand and wrist tendinopathy cases we have located have occurred earlier than that typically recorded for Achilles tendinopathy.²⁰ There is currently not enough data to draw conclusions as to why this might be the case, whether it is earlier identification or etiological. It also does not appear from the limited cases published that hand and wrist tendons, compared with the Achilles tendon, are more susceptible to tears after fluoroquinolones have been ceased. However, up to half of all Achilles tendon ruptures occur after fluoroquinolones have already been ceased.¹³ Clinicians should be aware of the ongoing possibility of fluoroquinolone-associated tendinopathy in patients who have had recent exposure to fluoroquinolones.

Fluoroquinolone-associated tendinopathy can very rarely present as a severe case requiring extensive reconstruction. Our patient had no significant medical history that would suggest specific vulnerability to fluoroquinolones but rather general vulnerability to his hand anatomy—a prior mutilating hand injury requiring tendon repair. Evidence from *in vitro* studies suggests that fluoroquinolones contribute to tendinopathy by inhibiting collagen maturation, reducing cell stability, and directly degrading matrix, any of which may be exacerbated by factors such as genetics and renal impairment.^{2,20} Although data on fluoroquinolone-associated tendinopathy in the hand specifically are scant, it is important to consider that prior tendon injury and its ongoing healing may have increased this patient's susceptibility to spontaneous tendon rupture on exposure to a prolonged fluoroquinolone course. Given the damage that may be caused to weakened tissue, clinicians should maintain a high index of suspicion of tendinopathy in patients on fluoroquinolones who have had previous tendon repairs.

The cardinal symptom of tendinitis is tenderness and pain, which may be on movement or also at rest, whereas tendon rupture pain is classically sudden and intense with laxity and loss of function in the affected joints. New or worsening pain while a patient is on a fluoroquinolone should lead the clinician to consider the possibility of tendinopathy. While tendon pain or damage may be due to other causes, including purely mechanical overuse or injury, fluoroquinolones can increase susceptibility to further injury and should be ceased immediately if any serious adverse effect such as tendinopathy is suspected.⁷ Treatment of tendinopathy is largely symptom driven, and tendinitis of the hand and wrist appears to resolve gradually after withdrawal of the fluoroquinolone without the need for further treatment. Acetaminophen may be effective for pain, and overuse of the affected region should be strictly avoided to prevent tendon rupture. Should tendon rupture or nerve entrapment occur, surgery may be necessary and should be tailored to the individual patient and injury.

Ethical Approval

This study was exempt from review by our institutional review board.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Auwaerter PG. Fluoroquinolones not first line: FDA advisory reinforces standard practice in ambulatory care. *Medscape*. <http://www.medscape.com/viewarticle/863778>. Published June 2, 2016. Accessed March 13, 2017.
2. Badal S, Her YF, Maher LJ III. Nonantibiotic effects of fluoroquinolones in mammalian cells. *J Biol Chem*. 2015;290(36):22287-22297.
3. Bailey RR, Kirk JA, Peddie BA. Norfloxacin-induced rheumatic disease. *N Z Med J*. 1983;93:590.
4. Cattaneo F, Serna M, Stoller R. Fluoroquinolone associated tendon rupture and bilateral tendinitis in a hemodialysis patient and two renal transplant recipients. *Kidney Int*. 1990;50:1429.
5. Chaslerie A, Bannwarth B, Landreau JM, Yver L, Begaud B. Ruptures tendineuses et fluoro-quinolones: un effet indésirable de classe. *Rev Rhum Mal Osteoartic*. 1992;59:297-298.
6. DeWolf MC, Warhold LG. Ciprofloxacin-induced extensor tendon rupture in the hand: a case report. *JBJS Case Connect*. 2015;5(2):e30. doi:10.2106/JBJS.CC.N.00059.
7. Food and Drug Administration. Drug Safety Communications. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM500591.pdf>. Published May 12, 2016. Accessed March 13, 2017.
8. Fraimow HS. Systemic antimicrobial therapy in osteomyelitis. *Semin Plast Surg*. 2009;23(2):90-99.
9. Gade ND, Qasi MS. Fluoroquinolone therapy in *Staphylococcus aureus* infections: where do we stand? *J Lab Physicians*. 2013;5(2):109-112.
10. Gillet P, Hestin D, Renoult E, Netter P, Kessler M. Fluoroquinolone-induced tenosynovitis of the wrist mimicking de Quervain's disease. *Br J Rheumatol*. 1995;34(6):583-584.
11. Jacoby L. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *J Emerg Med*. 2013;44(3):733-734.
12. Keating KN, Friedman H, Perfetto EM. Fluoroquinolone therapy for uncomplicated skin and skin structure infections. *Clin Drug Investig*. 2005;25(10):621-631.
13. Kim GK, Del Rosso JQ. The risk of fluoroquinolone-induced tendinopathy and tendon rupture. *J Clin Aesthet Dermatol*. 2010;3(4):49-54.
14. Lara RH, Wainstein EG, Guzmán LB. Tenosinovitis por ciprofloxacino caso clínico. *Rev Med Chile*. 1994;122:932-934.
15. Lee GC, Reveles KR, Attridge RT, et al. Outpatient antibiotic prescribing in the United States: 2000 to 2010. *BMC Med*. 2014;12:96.
16. Levadoux M, Carli PH, Gadea JF, De Mauleon de Bruyere P, Perre CL. Rupture iterative des tendons extenseurs de la main sous fluoroquinolones. *Ann Chir Main*. 1997;16(2):130-133.
17. Liang VY, Ghearing GR, Zivković SA. Carpal tunnel syndrome after ciprofloxacin-induced tendinitis. *J Clin Neuromuscul Dis*. 2010;11(3):165-166.
18. Rivero M, Otermin I, Pereda A, Cía M, Martínez M. Afectación articular y muscular secundaria a levofloxacino. *Rev Esp Quimioterap*. 2006;19(4):376-377.
19. Schwald N, Debray-Meignan S. Suspected role of ofloxacin in a case of arthralgia, myalgia, and multiple tendinopathy. *Rev Rhum Engl Ed*. 1999;66(7-9):419-421.
20. Stephenson AL, Wu W, Cortes D, Rochon PA. Tendon injury and fluoroquinolone use: a systematic review. *Drug Saf*. 2013;36:709-721.
21. Tsai W-C, Yang Y-M. Fluoroquinolone-associated tendinopathy. *Chang Gung Med J*. 2011;34:461-467.
22. Turker T, Kutz JE. Can oral levofloxacin cause of flexor digitorum profundus rupture? *Med Hypotheses*. 2011;77:696-697.
23. Wise BL, Peloquin C, Choi H, Lane NE, Zhang Y. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med*. 2012;125:1228.e23-1228.e28.