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Evidence of Tendinitis Provoked by Fluoroquinolone Treatment

A Case-Control Study

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Abstract

Objective: To investigate the association between the use of fluoroquinolone agents and the risk of tendinitis in a large population-based case-control study.

Methods: The study was performed by linking automated health databases from the Region of Lombardia, Italy. Cases were patients aged ≥18 years who had a hospital discharge diagnosis of non-traumatic tendinitis in 2002–3. For each case, up to five controls were randomly selected among those eligible for inclusion in the study. A conditional logistic regression model was used to estimate the odds ratio of tendinitis associated with the current, recent and past use of fluoroquinolones. Odds ratios were adjusted for exposure to other antibacterials and other drugs.

Results: 22 194 cases and 104 906 controls met the inclusion criteria. Current use of fluoroquinolones significantly increased the risk of tendon disorders as a whole (odds ratio [OR] = 1.7; 95% CI 1.4, 2.0), tendon rupture (OR = 1.3; 95% CI 1.0, 1.8) and rupture of the Achilles' tendon (OR = 4.1; 95% CI 1.8, 9.6). Concomitant use of corticosteroids and fluoroquinolones increased the risk of both tendon rupture (OR = 3.1; 95% CI 1.5, 6.3) and rupture of the Achilles' tendon (OR = 43.2; 95% CI 5.5, 341.1).

Discussion: Evidence that exposure to fluoroquinolones is associated with the sudden occurrence of tendinitis is supported by this large population-based study. We can estimate that a single case of rupture of the Achilles' tendon would occur for every 5958 persons treated with fluoroquinolones (95% CI 2148, 23 085). The corresponding number needed to harm is 979 (95% CI 122, 9172) for patients who concomitantly use corticosteroids and 1638 (95% CI 351, 8843) for those aged >60 years.

Conclusion: Clinicians should be aware of this adverse effect, and the increased risk for fluoroquinolone-associated tendinitis in elderly patients with corticosteroid use must be considered when these agents are prescribed.

Background

Fluoroquinolone antibacterial drugs have been in clinical use for up to 30 years and have been found to be well tolerated generally.[1] However, postmarketing surveillance has identified a series of adverse effects, mostly gastrointestinal disturbances, CNS disorders and skin reactions, associated with fluoroquinolone therapy.[2,3]

Anecdotal case reports have also associated the use of fluoroquinolones with tendinitis since the 1980s,[4,5] and in 1991 the first case of Achilles' tendon rupture in a fluoroquinolone-treated patient was published.[6] Subsequently, the number of reports of fluoroquinolone-associated tendinitis with and without rupture has increased[7-13] with the expanded use of fluoroquinolones.[14-16] Most of the original reports were from France,[17,18] and several case series coming from other countries have been published since 1991.[19-24] At present, approximately 3500 cases have been reported to the WHO Collaborating Centre for International Drug Monitoring.[25] Together, these signals have stimulated the attention of drug regulatory agencies.[26-28] Specific instances in which warnings have been issued by the registration authorities of several countries have particularly related to the treatment of elderly patients and those patients concomitantly receiving systemic corticosteroid therapy.

Experimental data have provided insights into the potential mechanism for this unusual form of drug toxicity. Because of their chelating properties,[29] fluoroquinolones may interact with regulating proteins of tenocytes and cause damage at the tendon structure.[30,31] In addition, apoptosis as the final event in the pathogenetic mechanism has been suggested recently.[32]

Even though the available evidence strongly suggests that tendinitis and tendon rupture are a fairly characteristic adverse effect of fluoroquinolone derivatives, the extension of the use of fluoroquinolones on the onset of tendon disorders has received surprisingly little attention in the epidemiological literature.[33-36]

We conducted a large population-based case-control study in order to assess the independent effect of the use of fluoroquinolone agents on the risk of non-traumatic tendinitis, as well as their joint action with concurrent exposure to corticosteroids.

Methods

Data were obtained from the health services databases of Lombardia, Italy. Lombardia is the largest Italian region, with a population of approximately 9 million people according to the Italian Population Census of 2001 (16% of the Italian population). Residents in Lombardia are covered by the National Health Service (NHS), which has been run since 1997 through a system of separate but electronically linkable databases, including the (i) archive of residents who receive health assistance from the NHS (practically the entire resident population), reporting demographic and administrative data; (ii) prescription drug database, which contains information on all the drugs reimbursable by the NHS and dispensed at the regional level; and (iii) hospital discharge database, which includes all admissions occurring in public and private hospitals.

Case patients were selected from the hospital discharge database from among the residents in Lombardia aged ≥18 years who had been hospitalised during the years 2002–2003 for tendon disorders, including synovitis and tenosynovitis (*International Classification of Diseases, 9th Edition* [ICD-9] code 727.0), and non-traumatic rupture of the tendon (727.6) [among these, non-traumatic rupture of the Achilles' tendon (727.67)]. Patients with a concomitant diagnosis of cancer (140–239), diabetes mellitus (250), thyroid disease (240–246), renal failure (584–586) or other disease of the musculoskeletal system and connective tissue (710–739) were excluded.

The date of first hospitalisation for a tendon disorder was referred to as the index date. Up to five controls for each case patient were randomly selected from the regional archive of residents after matching for sex, age, municipality of residence and index date. Cases and controls with a history of tendon disorders, gout, rheumatoid arthritis, rheumatic polymyalgia, other musculoskeletal diseases, renal failure, thyroid disease, diabetes, cancer and/or

Table I. Odds ratios of tendon disorders, tendon rupture and rupture of Achilles' tendon associated with current, recent and past use of fluoroquinolones in the Lombardia region, Italy, 2002–3

Fluoroquinolones[a]	Cases	Controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) [b]
Tendon disorders				
Non-use	21 354	101 953	1.0 (reference)	1.0 (reference)
Current use	246	623	1.9 (1.6, 2.2)	1.7 (1.4, 2.0)
Recent use	144	489	1.4 (1.2, 1.7)	1.3 (1.1, 1.6)
Past use	450	1 841	1.2 (1.0, 1.3)	1.1 (0.9, 1.2)
Tendon rupture				
Non-use	6 933	32 944	1.0 (reference)	1.0 (reference)
Current use	68	202	1.6 (1.2, 2.1)	1.3 (1.0, 1.8)
Recent use	55	154	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)
Past use	145	615	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Rupture of the Achilles' tendon				
Non-use	805	4 021	1.0 (reference)	1.0 (reference)
Current use	18	12	7.3 (3.5, 15.2)	4.1 (1.8, 9.6)
Recent use	4	10	2.1 (0.6, 7.3)	1.9 (0.5, 7.5)
Past use	13	48	1.3 (0.7, 2.5)	1.1 (0.5, 2.2)

a Exposure to fluoroquinolones is categorised as current use (exposure in the 15 days before or at index date), recent use (exposure 15–30 days before index date), past use (exposure 30–90 days before index date) and non-use (exposure >90 days before or no exposure in the 1-year period before the index date).

b Adjusted for the use of corticosteroids, other antibacterials and other drugs in the 30-day period before the index date.

AIDS and case patients with evidence of tendon disorders due to direct trauma were excluded.

The drug-dispensing history of fluoroquinolones (Anatomical Therapeutic Chemical [ATC] code: J01MA), other antibacterials for systemic use (J01 excluding J01MA), corticosteroids (H02) and other drugs (all the other ATC codes excluding J01 and H02) dispensed to case patients and controls during the 1-year period prior to the index date were collected from the prescription drug database. The drug exposure window was defined as the period between the dispensing date and the theoretical end date, which was calculated by adding the estimated duration of use to the starting date.

Exposure to fluoroquinolone agents at the index date was assessed and categorised into mutually exclusive groups of current use, recent use, past use and non-use. Current use was defined as exposure in the 15 days before or at the index date, recent use as exposure 15–30 days before the index date, past use as exposure 30–90 days before the index date and non-use as exposure >90 days before or no exposure in the 1-year period before the index date.

Exposure to other drugs was categorised as recent use, defined as exposure in the 30 days before or at the index date, and non-use, defined as exposure >30 days before or no exposure in the 1-year period before the index date.

The chi-squared (χ^2) test was used to assess the difference in the prevalence of drug exposure between patients and controls. Conditional logistic regression models were fitted to estimate odds ratios and 95% confidence intervals separately for tendon disorders, tendon rupture and rupture of the Achilles' tendon associated with each category of exposure to fluoroquinolones contrasted with non-use (reference category). Adjusted estimates were obtained by including in the model the main terms of concurrent exposure to other antibacterials, corticosteroids and other drugs. The homogeneity of the odds ratios across age classes (<60 and ≥60 years) was tested according to Mantel-Haenszel test.[37] In order to evaluate the joint effect of fluoroquinolones and concurrent treatments, interaction terms were included in the models and their significance was tested using the likelihood ratio test.[37] For all tested

hypotheses, two-tailed p-values <0.05 were considered to be significant.

Results

During the study period, 22 194 case patients and 104 906 controls met the inclusion criteria and were entered into the study. Among the included case patients, 14 993 were hospitalised for synovitis and tenosynovitis and 7201 for non-traumatic tendon rupture (among these, 840 for rupture of the Achilles' tendon).

Most of the case patients were women (63.5%), and the mean age was 55.9 years (matching variables). Compared with controls, case patients had a higher prevalence of exposure to fluoroquinolones (3.8% vs 2.8%; p <0.001), corticosteroids (2.0% vs 1.4%; p <0.001) and other drugs (19.9% vs 19.3%; p = 0.040) dispensed at any time in the 90-day period preceding the index date. Conversely, case patients and controls did not differ in the use of other antibacterials (10.1% vs 9.7%; p = 0.068).

Table I shows the crude and adjusted odds ratios for each outcome. Potential confounders only marginally affected the odds ratios of interest, since no noteworthy differences in crude and adjusted estimates appeared. The risk of both tendon disorders as a whole and tendon rupture was significantly higher among current and recent users of fluoroquinolones. The odds ratios of rupture of the Achilles' tendon were also associated with current and recent exposure to fluoroquinolones. However, there was statistical evidence of association only for current use. The risk associated with past use did not seem to differ from the risk associated with non-use.

In the subsequent analyses, current and recent users of fluoroquinolones were combined (and referred to as recent users) and contrasted with past users and non-users combined (referred to as non-users).

Table II provides the adjusted odds ratios stratified by age for each outcome. Exposure to fluoroquinolones within 30 days before or at the index date was associated with the onset of tendinitis in both patients aged <60 years and those aged ≥60 years. The increased risk for both tendon disorders and tendon rupture was similar across the two classes of age (p = 0.691 and p = 0.694, respectively), whereas the odds ratio for rupture of the Achilles' tendon was significantly higher in patients aged ≥60 years than in patients aged <60 years (p = 0.009).

Table III shows the independent and combined effects of fluoroquinolones and corticosteroids on the risk of each outcome. There is evidence that recent exposure to either fluoroquinolones or corticosteroids acted as an independent risk factor for tendinitis. In fact, significant effects of recent exposure to corticosteroids appeared in people who did not use fluoroquinolones within 30 days before the index date. Analogously, significant effects of recent exposure to fluoroquinolones appeared in people who did not use corticosteroids within 30 days before the index date. No noteworthy departure from the multiplicative structure of interaction between the considered factors was observed for tendon disorders as a whole (p = 0.070). In fact, the effects of current or recent exposure to fluoroquinolones were substantially homogeneous in people who recently used and in those who did not use corticosteroids. Conversely, significant departures from the multiplicative structure of interaction were

Table II. Adjusted odds ratios of tendon disorders, tendon rupture and rupture of Achilles' tendon associated with recent use of fluoroquinolones according to age in the Lombardia region, Italy, 2002–3

Outcome	Age <60 years			Age ≥60 years	
	cases	controls	odds ratio (95% CI)[a]	cases	controls
Tendon disorders	160	432	1.5 (1.2, 1.7)	230	680
Tendon rupture	41	107	1.6 (1.1, 2.3)	82	241
Rupture of the Achilles' tendon	6	10	2.7 (1.0, 7.4)	12	2

a Odds ratio of recent use (exposure in the 30 days before or at index date) contrasted with non-use (exposure >30 days before or no exposure in the 1-year period before the index date) of fluoroquinolones adjusted for use of corticosteroids, other antibacterials and other drugs in the 30-day period before the index date.

Table III. Independent and combined actions of fluoroquinolones and corticosteroids on the risk of tendon disorders, tendon rupture and rupture of the Achilles' tendon in the Lombardia region, Italy, 2002–3

Fluoroquinolones[a]	Corticosteroids[a]	Cases	Controls	Adjusted odds ratio (95% CI)[b]
Tendon disorders				
Non-use	Non-use	21 384	102 423	1.0 (reference)
Recent use	Non-use	366	1 048	1.7 (1.5, 1.9)
Non-use	Recent use	420	1 371	1.5 (1.3, 1.7)
Recent use	Recent use	24	64	1.8 (1.1, 2.9)
Tendon rupture				
Non-use	Non-use	6 921	33 119	1.0 (reference)
Recent use	Non-use	110	336	1.6 (1.3, 2.0)
Non-use	Recent use	157	440	1.7 (1.4, 2.1)
Recent use	Recent use	13	20	3.1 (1.5, 6.3)
Rupture of the Achilles' tendon				
Non-use	Non-use	796	4 023	1.0 (reference)
Recent use	Non-use	13	21	3.0 (1.5, 6.0)
Non-use	Recent use	22	46	2.1 (1.2, 3.6)
Recent use	Recent use	9	1	43.2 (5.5, 341.1)

a Exposure to fluoroquinolones and corticosteroids categorised as recent use (exposure in the 30 days before or at index date) and non-use (exposure >30 days before or no exposure in the 1-year period before the index date).

b Adjusted for use of other antibacterials and other drugs in the 30-day period before the index date.

observed for both tendon rupture ($p = 0.029$) and rupture of the Achilles' tendon ($p = 0.049$). In fact, the effects of recent exposure to fluoroquinolones were much higher in people who recently used corticosteroids than in those who did not use corticosteroids.

Discussion

Based on this large population-based case-control study, patients currently treated with fluoroquinolones are at 1.7-, 1.3- and 4.1-fold increased risk of developing tendon disorders as a whole, tendon rupture and rupture of the Achilles' tendon, respectively. Although case patients had a higher prevalence of exposure to other drugs than controls, adjustment for these factors did not wash out the association with tendinitis. The lack of evidence of increased risk associated with less recent exposures to fluoroquinolones supports the causal role of such drugs on the risk of tendinitis. Finally, the present findings showed that concurrent exposure to corticosteroids may act as a multiplier effect on the risk of tendon rupture associated with recent exposure to fluoroquinolones.

Compared with fluoroquinolone-associated tendon disorders described from published case series, patients included in the present study who were currently or recently exposed to fluoroquinolones had a similar mean age at diagnosis (63.2 years vs 63 years),[18] similar median latency period between the start of fluoroquinolone treatment and occurrence of tendon rupture (16 days vs 2 weeks),[20] and comparable prevalence of concomitant use of corticosteroids (15.2% vs 20%).[22]

Despite the large volume of case-based evidence, surprisingly few and contrasting studies based on formal epidemiological designs have been performed on this topic. Current use of fluoroquinolones was found to be associated with a 3- to 4-fold increased risk of Achilles' tendinitis or Achilles' tendon ruptures in epidemiological studies using data from general practice databases.[33-35] Increased risk among the elderly and in corticosteroids users was also reported from these studies.[33-35] Consistently, our study showed both a 4-fold increased risk of Achilles' tendon rupture among current fluoroquinolone users and evidence that increased risk mainly affects elderly patients receiving concomitant corticosteroids. However, these results

differ noticeably from those of a recent case-control study using data from health insurance claims, which reports a moderate and not significant elevation in risk of Achilles' tendon rupture of 1.2-fold in fluoroquinolone users, without any evidence of interaction with the concomitant use of corticosteroids.[36] Detection bias, other forms of selection bias and misclassifications were evocated in explaining this unusual finding.

Because general practice databases were used in studies published before ours, it has been hypothesised that certain exposures might serve to heighten suspicions and lead to diagnostic work-up or referral. However, this possibility seems remote in the present study given the linkage between drug prescriptions and hospital discharge databases. It is possible that only a selected fraction of patients affected by tendon disorders will be captured by general practice databases; this scenario may well have occurred in our study, because diagnoses were drawn from archives of hospitalised patients. This would explain why our estimate of the effect of fluoroquinolones on the risk of tendon disorders (1.7; 95% CI 1.4, 2.0) is lower than that reported from a previous epidemiological study that was based instead upon a general practice archive (3.7; 95% CI 0.9, 15.1).[33] However, because of the severity of Achilles' tendon ruptures, we can assume a nearly complete ascertainment of this condition. Furthermore, although only non-traumatic Achilles' tendon ruptures were included, the observed incidence rate (0.5 cases per 10 000 person-years, as derived from 840 cases that occurred over 2 years from 7.7 million inhabitants) is similar to that reported from previous population-based studies.[38-41]

Differential misclassification of tendon disorder diagnosis has been suspected when general practice databases are used, in a way that appears to mimic clinical expectations. However, this is unlikely to have happened in our study given the linkage between independent databases. Rather, misclassification of subjects according to their disease and exposure status as a result of errors in identification, diagnostic and therapeutic codings, and uncertain compliance of patients with their treatment[42] might affect the validity of the current estimates. However, since misclassification of both diagnosis and exposure is not expected to be differential, i.e. respectively independent from exposure and disease status, it generally leads to bias towards underestimation of the true effect.[43]

Among the different fluoroquinolones, pefloxacin and ofloxacin have been connected most frequently with tendon disorder diagnosis from case-based reports,[19,20] and ofloxacin has shown a stronger association with Achilles' tendinitis according to some epidemiological studies.[22,33,35,44] In the current setting, about 70% of controls who used fluoroquinolones were treated with ciprofloxacin or levofloxacin. No evidence of heterogeneous effects associated with exposure to these drugs appeared (odds ratio [OR] = 1.9, 95% CI 1.5, 2.3 and OR = 1.5, 95% CI 1.3, 1.9, respectively; p = 0.470). Because of the low number of controls who had been recently exposed to other drugs belonging to the fluoroquinolones class, the investigation of the hypothesised differential effects is hampered in the current study.

Current and recent exposure to fluoroquinolones was set at 15 and 30 days, respectively, before the index date in the present study. A sensitivity analysis concerning different exposure windows revealed that the risk of tendinitis increased as the exposure window got narrower, reaching the maximum value for a time window of 15 days before the onset of tendinitis. However, power considerations related to the small number of exposed subjects suggested that we use a time window of 30 days when running stratified analyses according to age and corticosteroid use. This will likely lead to an underestimation of the corresponding effects.

Because urinary and respiratory tract infections are not risk factors for tendon disorders, it is unlikely that confounding by indication affected the current estimates. Renal insufficiency, rheumatological disease, especially rheumatoid arthritis, hyperparathyroidism, musculo-skeletal disorders and diabetes are well established risk factors for tendinitis and tendon rupture.[39,41,45,46] Accordingly, patients affected by these conditions were excluded

from our study. Patients affected by other conditions that seriously impair general health status and require intensive pharmacological treatment and those with tendon disorders due to direct trauma were also excluded. Exposure to corticosteroids is a common antecedent of Achilles' tendon rupture and is thought to increase the risk of rupture through tendon atrophy and weakening.[47-51]

The use of corticosteroids was found to be an independent risk factor for Achilles' tendon rupture in our study and, therefore, the effect of fluoroquinolones on the risk of the investigated condition was adjusted for. In order to avoid confounding due to the differential attitude of case patients and controls who have frequent contact with health services (e.g. home residence, frequent physician contact and hypochondriasis), the estimates were also adjusted for the concomitant prescription of other antibacterials and other drugs, which may be considered a proxy for general practitioner contact. However, other uncontrolled confounders might play a role in explaining some of the results from our study. For instance, the effects of obesity and hyperlipidaemia, as potential causes of tendon rupture,[39,40,46] were not controlled because of a lack of specific data sources.

Conclusions

The current study confirms that Achilles' tendon rupture is a common adverse reaction to treatment with fluoroquinolones. We can estimate that a single case would occur for every 5958 persons treated with fluoroquinolones (95% CI 2148, 23 085).[52] The corresponding number needed to harm is 979 (95% CI 122, 9172) for patients who concomitantly use corticosteroids and 1638 (95% CI 351, 8843) for those aged >60 years. The clinical impact of fluoroquinolone use on the onset of less severe forms of tendon disorders is actually unknown, but it is expected to be even higher. Clinicians should be aware of this adverse effect, and concurrent corticosteroid use, especially in elderly patients, must be considered when these agents are prescribed.

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