Achilles tendinitis associated with fluoroquinolones

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Aims To determine whether there is an association between use of fluoroquinolones and tendinitis in a large population under everyday circumstances.

Methods A retrospective cohort study was carried out in a dynamic population. Data came from the IPCI-database which consists of all data on consultations, morbidity, prescriptions and other interventions, as registered by GPs in a source population of approximately 250 000 persons. For this study data were collected from 41 general practices in the period from January 1st, 1995 through December 31st, 1996. All persons treated with either fluoroquinolones, amoxicillin, trimethoprim, cotrimoxazole or nitrofurantoin were followed from the first day of treatment until the outcome of interest, death, transfer to another practice, or end of the study period, whichever came first. The risk window was defined as the legend duration +1 month. Potential cases were defined as a registration of a tendinitis or tendon rupture. Patients with a history of tendinitis or tendon rupture, preceding trauma or inadequate diagnoses were excluded on the basis of a review of the patient profiles and additional clinical data, blinded as to the exposure status. Results were adjusted for age, gender, concurrent corticosteroid exposure and number of GP visits.

Results There were 1841 users of fluoroquinolones and 9406 users of the other antibacterial drugs with an average duration of 9 and 7 days, respectively. Tendinitis or tendon rupture was registered in 97 profiles, but after review only 22 complied with the case definition. The adjusted relative risk of tendinitis to fluoroquinolones was 3.7 (95%CI: 0.9–15.1) for Achilles tendinitis and 1.3 (95%CI: 0.4–4.7) for other types of tendinitis. Achilles tendinitis to ofloxacin had a relative risk of 10.1 (95%CI: 2.2–46.0) and an excess risk of 15 cases per 100 000 exposure days.

Conclusions Although the numbers in our study are small, our results suggest that some fluoroquinolones may increase the risk of Achilles tendinitis, and that this risk increase is highest for ofloxacin.

Keywords: Achilles tendinitis, cohort study, fluoroquinolones, pharmacoepidemiology, tendinitis

Introduction

In the past few years, there has been a marked increase in the number of spontaneous reports of tendinitis associated with fluoroquinolones [1–7]. In the vast majority of cases, the Achilles tendon was affected with symptoms compatible with painful tendinitis or with rupture, usually during the first 2 weeks of treatment. Fluoroquinolones form a relatively new class of antibacterial agents which act by inhibiting bacterial DNA gyrase [8]. The most frequently observed adverse effects are of gastro-intestinal origin, followed by CNS disorders and skin reactions [8]. Although in several case reports tendinitis has been attributed to fluoroquinolones, the epidemiological confirmation of the association is scanty. In order to assess whether there is an association between fluoroquinolones and tendinitis, and to determine the incidence and relative risk of tendinitis to the different products, we conducted a retrospective cohort study in a large population under everyday circumstances.

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Methods

Data source

Data were obtained from the Integrated Primary Care Information (IPCI) system, a research-orientated database

with data from computerized patient records of general practitioners (GPs) throughout the Netherlands which was developed by the Department of Medical Informatics of the Erasmus University Medical School. The database includes all demographic information, patient complaints, symptoms, laboratory tests, diagnoses, discharge and consultant letters, and prescription details (including drug name, dosage form, dose, quantity prescribed, and indication). GPs write the prescriptions directly from the computer, thus ensuring automatic recording. Medication codes are based on the national database of drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy. A modification of The International Classification for Primary Care [9] is the coding system employed for patient complaints, diagnoses, and indications but these can also be entered as free text. At present, the IPCI-project monitors a population of about 250 000 patients on a continuous basis. The data used for this study were collected from 41 general practices in the period between January 1st, 1995 and December 31st, 1996.

Cohort definition

The cohort consisted of all patients of 15 years and older with a permanent status who were treated in the study period with one of the following antibacterial drugs: fluoroquinolones (index group), amoxicillin, trimethoprim, cotrimoxazole and nitrofurantoin (reference group). The latter four drugs were chosen as a reference because these are commonly used drugs with a well-known safety profile, and have not been associated with tendinitis. Subjects had to have a computer-recorded history of at least 3 months duration prior to the date of first prescription in order to be eligible to participate in this study. All coded prescriptions were considered with the exclusion of dermatological and ocular preparations. The patients entered the study cohort on first prescription of one of the study drugs at which time contribution to person-time experience started. Subjects were followed until the outcome of interest, transfer to another practice, death, or end of the study period, whichever came first. Patients were excluded if gender, age, or dosage of the study drugs were unknown, if they were chronic users of the drugs under study (more than 60 days in 1 year), and if there was a history of inflammatory joint disease (e.g. rheumatoid arthritis, SLE), Reiter's syndrome, polymyalgia rheumatica, gout or AIDS.

Exposure and outcome definition

For each prescription, the legend duration was calculated as the amount of prescribed drug divided by the daily dose. The total exposed period of each subject was calculated as the sum of the legend durations, corrected for refill prescriptions. The risk period was defined as the exposed period plus 1 month. The month was added because any increased risk during exposure will have a carry-over effect and because a notification in GP-records may be delayed when patients present themselves with tendinitis several days after onset. Concomitant users of fluoroquinolones and one of the reference drugs during this risk period were excluded.

To ensure maximal sensitivity and specificity, we followed a two-step selection procedure of case-finding (step 1) and case-validation (step 2). In step 1, potential cases of the outcome of interest were defined as the registration of one or more of the diagnoses or symptoms mentioned in Table 1 within the risk period. Moreover, all records were studied for a notification of 'tendinitis', 'tendon disorder', 'tendon rupture', 'coup de fouet' or 'pain upper leg' in the free text of each patient file. In step 2, for all selected patients a patient profile was generated and printed, where all prescriptions, GP medical diagnoses, laboratory results, hospital referrals and GP remarks were listed. The exposure to the study drugs in these patient profiles was blinded. Following an independent review of the patient profile by two GPs, patients were excluded if the patient had a history of tendinitis or tendon rupture before use of the study drugs, if another cause of the tendinitis was likely (e.g. trauma), or if the diagnosis was wrong (e.g. bursitis). In case of disagreement, the data were independently reviewed by a third medical practitioner. To confirm the adequacy of the validation procedure, the GPs of potential cases were sent a questionnaire requesting details of some of the clinical features and any correspondence available related

Table 1 List of ICPC-codes included in the case definition.

ICPC-code	*Symptom/Diagnosis*
L81	Other musculoskeletal injuries
L81.1	Coup de fouet
L81.3	Tendon rupture
L92	Shoulder syndrome
L92.2	Tendinitis supraspinatus
L92.3	Tendinitis infraspinatus
L92.4	Tendinitis subscapularis
L92.5	Tenosynovitis biceps brachii
L92.6	Lesion tendon m. supraspinatus
L92.8	Other shoulder syndromes
L93	Epicondylitis lateralis
L99	Other diseases of the musculoskeletal system
L99.2	Tendovaginitis stenosans
L99.3	Other tendovaginitis/tendinitis
L99.5	Epicondylitis medialis
L99.9	Other diseases of the musculoskeletal system

to the diagnosis of interest. All patients' personal identifiers were suppressed before sending.

Analysis

The first outcome-related event that occurred was used in the analyses. The incidence density (ID) was calculated by dividing the number of events occurring in the risk windows by the total risk period, and was expressed as the number of events per 100 000 days at risk. Incidence densities for exposure to fluoroquinolones were compared with those for the reference drugs. The relative risk (RR) of tendinitis was calculated as an incidence density ratio, dividing the two incidence densities. The excess risk was calculated by subtracting the incidence densities in index and reference group. Confidence (95%) intervals for the crude and adjusted relative risks were estimated with Poisson regression analysis. Adjusted estimates of the RR were controlled for the potentially confounding effects of gender, age, number of GP visits and concurrent corticosteroid use.

Results

In the study period, 11 812 patients of 15 years and older received 18 428 prescriptions for the study drugs. Of these, 786 patients were excluded because dosage was unknown ($n=34$), because of concomitant use of fluoroquinolones and the reference drugs in the risk period ($n=653$) or because they were chronic user ($n=99$). Furthermore, 226 patients were excluded because they had a history of rheumatoid arthritis ($n=76$), SLE ($n=3$), polymyalgia rheumatica ($n=28$), gout ($n=118$) or AIDS ($n=1$). Hence, the study population consisted of 10 800 patients. During the study period, there were 1841 users of fluoroquinolones and 9406 users of the other antibacterial drugs (fluoroquinolones as well as one of the reference drugs may have been prescribed to the same patient outside the risk period), with an average duration of 9 and 7 days, respectively (Table 2). In total, 418 patients received 500 prescriptions for ofloxacin, 456 patients received 556 prescriptions for ciprofloxacin and 1030 patients received 1362 prescriptions for norfloxacin, with an average duration of 10, 9 and 8 days, respectively. Most index and reference drugs were used for urinary or respiratory tract infections at the recommended daily dosage. There was no significant difference in indication between index and reference group. The reference group consisted of relatively more female patients. The mean age in the index group was higher; patients in the index group visited the GP more often, and had a higher prevalence of renal failure (Table 2). During the total risk period of 548 919 days, possible cases of tendinitis or tendon rupture were registered in 97 patient profiles. After more extensive review of the computerized profiles of these potential cases by the medical reviewers, 68 (70%) cases were excluded from further analysis: 26 (38%) because the diagnosis was not tendinitis but mostly bursitis, 12 (18%) because tendinitis was probably caused by a trauma and 30 (44%) because there was a history of tendinitis or tendon rupture before intake of the study drugs. Concerning the remaining 29 cases, questionnaires were sent to the GPs which were all returned after some reminders. After blinded review, 7 additional patients were excluded: 2 cases because the diagnosis was not tendinitis, and 5 because tendinitis was caused by trauma. Consequently, 22 cases (all tendinitis; no rupture) complied with the case definition. In 8 of these patients, the Achilles tendon was affected. Of the 22 cases, 7 occurred during fluoroquinolones and 15 during use of a reference drug. The incidence density of tendinitis during fluoroquinolones was 7.74 per 100 000 days at risk and 3.27 for the reference drugs, which is compatible with a RR of 2.4 (95% CI: 0.96–5.80). Ofloxacin had a significantly increased crude RR of tendinitis of 6.5 (95%CI: 2.14–19.45), which declined after adjustment to 4.9 (95%CI: 1.57–15.06). No significant association was found for ciprofloxacin and norfloxacin (Table 3). After stratification for Achilles tendinitis and other types of tendinitis, fluoroquinolones as a group had an elevated RR of Achilles tendinitis of 4.4 (95% CI: 1.27–20.27), which declined after adjustment to 3.7 (95% CI: 0.93–15.14), while no association was found for the other types of tendinitis. Ofloxacin was associated with an increased RR of 10.1 for Achilles tendinitis (95% CI: 2.20–46.04), whereas no association was found with the other types of tendinitis for the different fluoroquinolone agents (Table 3). The risk difference between fluoroquinolones and the reference drugs was 4 cases per 100 000 days for tendinitis, and 4 cases per 100 000 days for Achilles tendinitis. Ofloxacin was associated with a risk increase of 15 cases per 100 000 days. A duration-or dose effect relationship could not be assessed as almost all courses were given for similar short periods and because the large majority of fluoroquinolone users took the recommended daily dose.

Discussion

In this study, we found that the risk of tendinitis with fluoroquinolones was higher than the risk with a reference group of four commonly used antibacterial agents with a known safety profile. As these are not known to cause tendinitis, they represent the background risk and even if some actually cause tendinitis, this would tend to underestimate the RR of fluoroquinolones. Ofloxacin had the strongest association with Achilles tendinitis. Although age, gender, and number of visits to the GP

Table 2 Characteristics of the patient in the index group and in the reference group.

	Fluoriquinolones (index group)	*Amoxicillin, trimethoprim, co-trimoxazole and nitrofurantoin (reference group)*	
Number of users	1841 (100.0%)	9406 (100.0%)	
Gender			
Male	664 (36.1%)	2693 (28.6%)	
Female	1177 (63.9%)	6713 (71.4%)	$P<0.001$
Mean age (years)	53	45	$P<0.001$
GP visits (mean/year)	11.6	9.6	$P<0.001$
Concomitant corticosteroid use	85 (4.6%)	396 (4.2%)	$P>0.05$
Renal failure	36 (1.9%)	66 (0.7%)	$P<0.001$
Total exposure period	19 751 days	81 789 days	
Total risk period	90 435 days	458 484 days	
Mean treatment cycle	8.5 days	6.8 days	
Mean observation period/patient	1.75 person years	1.78 person years	

Table 3 The incidence densities stratified for achilles tendinitis and other tendinopaties among the drugs under study and relative risks stratified for achilles tendinitis and other tendinopaties.

	Cases	*Risk period*	*ID/100 000 days*	RR_{crude}	*(95% CI)*	$RR_{adjusted}$	*(95% CI)*
All tendinitis							
Reference drugs★	15	458 484	3.27	1.0	–	1.0	–
Fluoroquinolones	7	90 435	7.74	2.4	(0.96–5.80)	2.1[#]	(0.83–5.09)
Ofloxacin	4	18 944	21.11	6.5	(2.14–19.45)	4.9[#]	(1.57–15.06)
Ciprofloxacin	2	20 487	9.76	3.0	(0.68–13.05)	2.2[#]	(0.50–9.88)
Norfloxacin	1	51 004	1.96	0.6	(0.08–4.54)	0.6[#]	(0.08–4.59)
Achilles tendinitis							
Reference drugs★	4	458 237	0.87	1.0	–	1.0	–
Fluoroquinolones	4	90 371	4.43	5.1	(1.27–20.27)	3.7[#]	(0.93–15.14)
Ofloxacin	3	18 929	15.85	18.2	(4.06–81.12)	10.1[#]	(2.20–46.04)
Ciprofloxacin	1	20 461	4.89	5.6	(0.63–50.09)	2.8[#]	(0.30–25.18)
Norfloxacin	0	50 981	–	–	–	–	–
Other tendinopathies							
Reference drugs★	11	458 426	2.40	1.0	–	1.0	–
Fluoroquinolones	3	90 362	3.32	1.4	(0.39–4.96)	1.3[$]	(0.36–4.71)
Ofloxacin	1	18 886	5.29	2.2	(0.28–17.10)	2.0[$]	(0.25–16.08)
Ciprofloxacin	1	20 472	4.88	2.0	(0.26–15.77)	1.8[$]	(0.23–14.41)
Norfloxacin	1	51 004	1.96	0.8	(0.11–6.31)	0.8[$]	(0.10–6.05)

[#]Adjusted for age, gender, GP visits and concomitant corticosteroid use.

[$]Adjusted for age, gender and GP visits.

Amoxicillin, cotrimoxazol, nitrofurantoin or trimethoprim.

Significant RR and 95%-confidence limits are given in italics and bold printing.

differed significantly between the fluoroquinolone users and the users of other antibacterial drugs, adjustment for these factors did not eliminate the association with tendinitis. None of the cases had renal failure, which has been suggested as a possible risk factor for tendinitis [7]. Use of corticosteroids, a suggested risk factor for tendon rupture, was not related to tendinitis in this study.

The validity of epidemiological studies may be endangered by selection bias, information bias, or confounding. As the association between fluoroquinolones and tendinitis was only recently widely recognized and as proven risk factors for tendinitis, such as physical training, are not a contra-indication for fluoroquinolones selection bias is unlikely. One of the advantages of a study using automated GP data is that information on disease and exposure are gathered by GPs who are not aware of the research hypothesis at the time of registration. Hence recall bias or other types of information bias are not very likely in this study. To avoid observer bias we conducted a review of the patient profiles which was blinded to exposure status. Another important aspect concerning the validity of follow-up studies with automated data resources is the proportion of unidentified eligible cases (false negatives) through the initial computerized search. We

have tried to minimize this problem by performing not only a search on a wide range of ICPC-codes but also a text string search in the database. This explains in part why only 22 out of 97 possible cases passed the validation procedure. In the IPCI-project information is gathered only from GPs who are fully automated and do not use paper resources. Even if cases of tendinitis have been misclassified, misclassification was probably random. Hence, this will not affect the RR in a cohort study but might have some effect on the risk difference. Confounding by indication in this study is not very likely, as there was no association with indication, and because urinary-and respiratory tract infections are not a risk factor for tendinitis.

Apart from several case reports [1–7], a large case series in France reported on 100 cases which had been notified between 1985 and 1992 [10]. The Achilles tendon was affected in 96 patients and tendon rupture occurred in 31 persons. The average time between the start of the treatment and the onset of the symptoms was 13 days (range, 1–90 days). Long-term corticosteroid therapy was an associated risk factor. Pierfitte estimated the incidence rate of tendinitis among fluoroquinolone users at 15–20 per 100 000 prescriptions [11]. Others concluded that there was no increased risk of Achilles tendon rupture to ciprofloxacin [12]. In a study with prescription-event monitoring, the frequency rate of tendinitis, tenosynovitis or tendon rupture was 1/11 000 patients for ciprofloxacin, 3/11 000 patients for norfloxacin and 11/11 000 patients for ofloxacin, respectively [13]. Although the relatively high rate with ofloxacin is in line with our results, the incidence in our study is higher.

The pathophysiological mechanism linking tendinitis to fluoroquinolones remains unknown. Experimental data are restricted to cartilage injuries in immature animals [14, 15]. Some authors described the histological findings in damaged Achilles tendons and considered these changes to be due to an ischaemic process [16]. Other have considered the tendon disorders to be caused by a toxic effect on collagen fibres [17]. Furthermore, a role of mechanical factors has been suggested [18], and an autonomic nervous system disturbance or immuno-allergic phenomenon cannot be excluded [16].

Although the findings of our study support the hypothesis that fluoroquinolones are associated with tendinitis, definite conclusions should be drawn cautiously. Numbers of patients with tendinitis in our study are relatively small and follow-up is limited to only 2 years. In addition, the 95% confidence intervals of the risk estimates of the different fluoroquinolones do not differ significantly. Nevertheless, our results indicate that ofloxacin is strongly associated with Achilles tendinitis.

In conclusion, our results suggest that the risk of Achilles tendinitis to fluoroquinolones, especially ofloxacin, is higher than the risk to the other antibacterial drugs. To our knowledge, this is the first epidemiological study which demonstrates an increased risk. It should be emphasized, however, that the absolute numbers in our study are small and that an extra number of cases of Achilles tendinitis of 15 per 100 000 days may be acceptable when prescribed for severe infections.

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