ORIGINAL INVESTIGATION

Increased Risk of Achilles Tendon Rupture With Quinolone Antibacterial Use, Especially in Elderly Patients Taking Oral Corticosteroids

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Background: In several case reports, the occurrence of Achilles tendon rupture has been attributed to the use of quinolones, but the epidemiologic evidence for this association is scanty.

Methods: We conducted a population-based case-control study in the General Practice Research Database in the United Kingdom during the period 1988 through 1998. Cases were defined as all persons who had a first-time recording of an Achilles tendon rupture, and who had at least 18 months of valid history before the index date. As a control group, we randomly sampled 50 000 patients with at least 18 months of valid history who were assigned a random date as index date.

Results: We identified 1367 cases that met the inclusion criteria. The adjusted odds ratio (OR) for Achilles tendon rupture was 4.3 (95% confidence interval [CI], 2.4-7.8) for current exposure to quinolones, 2.4 (95% CI, 1.5-3.7) for recent exposure, and 1.4 (95% CI, 0.9-2.1) for past exposure. The OR of Achilles tendon rupture was 6.4 (95% CI, 3.0-13.7) in patients aged 60 to 79 years and 20.4 (95% CI, 4.6-90.1) in patients aged 80 years or older. In persons aged 60 years and older, the OR was 28.4 (95% CI, 7.0-115.3) for current exposure to ofloxacin, while the ORs were 3.6 (95% CI, 1.4-9.1) and 14.2 (95% CI, 1.6-128.6) for ciprofloxacin and norfloxacin, respectively. Approximately 2% to 6% of all Achilles tendon ruptures in people older than 60 years can be attributed to quinolones.

Conclusions: Current exposure to quinolones increased the risk of Achilles tendon rupture. The risk is highest among elderly patients who were concomitantly treated with corticosteroids.

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SINCE THEIR introduction in the mid-1980s, quinolones have been associated with tendon disorders, in particular with Achilles tendinitis and Achilles tendon rupture.[1-4] During the past years, the number of case reports has risen, possibly because of the increased use of quinolones.[5-8] Rupture of the Achilles tendon is a serious condition that often requires surgical treatment. Apart from several case reports and case series, one case-control study suggested that quinolones increase the risk of Achilles tendon rupture.[9]

Quinolones are antibacterial agents that act by inhibiting bacterial DNA gyrase.[10] These drugs are among the most frequently prescribed antibacterial agents because of their broad spectrum, relatively few serious adverse reactions, and good oral absorption.[11,12] The recent approval of quinolones with a broader antibacterial spectrum and the possibility of once-daily dosing may lead to even more frequent use of these drugs.[13]

We conducted a population-based case-control study using the computerized records from the General Practice Research Database to quantify the risk of Achilles tendon rupture from quinolones, and to study the role of concomitant risk factors.

METHODS

SOURCE OF DATA

The study was based on information derived from the General Practice Research Database, which contains computerized medical information of approximately 8 million inhabitants in the United Kingdom. All information is recorded on an ongoing daily basis by general practitioners (GPs) who use office computers provided by In Practice Systems, London, England (formerly Value Added Medical Products), and who have agreed to provide data for research purposes. The database is currently owned by the Medicines Control Agency, London. Data recorded include patient demographics, symptoms, diagnoses, referrals, hos-

pitalizations, and vital status. Referral letters from consultants and hospital records are kept by the GP in a manual file. The GP generates prescriptions directly from the computer, thus ensuring automatic recording. A modification of the Oxford Medical Information System classification and Read codes (for some practices) is used to enter medical diagnoses, and a coded drug dictionary based on the UK Prescription Pricing Authority dictionary is used for the recording of prescriptions. The recorded information on drug exposure and diagnoses in the General Practice Research Database is of high quality and adequate for drug safety studies.[14,15]

SELECTION OF CASES AND CONTROLS

The study population consisted of all subjects aged 18 to 95 years with permanent registration status at the index date (defined below), and 18 months of up to standard history. During the study period (January 1, 1988, to January 1, 1999), we identified all subjects who had a first-time occurrence of a potential Achilles tendon rupture (Oxford Medical Information System: 845 B, 7339 E, 7339 TT). Cases were excluded if they had less than 18 months of history; a history of cancer, drug abuse, alcoholism, or AIDS; or a hospital admission in the month before the index date. For the remaining potential cases, the medical history was reviewed, without knowledge of drug exposure. We excluded cases if the diagnosis was other than Achilles tendon rupture (eg, bursitis and Achilles tendinitis without rupture) or if the rupture was due to major trauma, such as fractures, falling from a stairs, or car accidents. Indirect trauma, for instance, due to exercise, was not excluded. The date of diagnosis of Achilles tendon rupture was used as the index date.

A group of 50 000 persons were randomly selected from the practices where the cases were registered, and a random date during the study period was assigned to each as the index date. All inclusion and exclusion criteria for the selection of cases were also used for the selection of control subjects.

EXPOSURE DEFINITION

For each subject, we identified exposure to oral or parenteral quinolones before the index date. Exposure was categorized in 3 mutually exclusive categories based on the time since last exposure. We did this to explore the effect of both short-term (current use) and delayed (recent and past use) effects of quinolones. A person was classified as currently exposed to quinolone if the index date fell within the period between the start of the quinolone treatment and the prescription length plus 30 days. We added this period of 30 days because the majority of quinolone-associated Achilles tendon rupture occurred within 1 month after starting a 7- or 10-day course of treatment at a moment on which the course had already been finished.[16] A person was classified as recently exposed to quinolone if he or she was not currently exposed and the end of the calculated prescription length was less than 180 days before the index date. A person was classified as exposed in the past if he or she was not currently or recently exposed and the end of the calculated prescription length was less than 18 months before the index date. All persons who did not use any of the study drugs in the 18 months preceding the index date were considered nonexposed.

To study a dose-effect relationship, the prescribed daily dose was expressed in defined daily dose (DDD) equivalents to be able to proxy the effect of equipotent doses of all quinolones on the occurrence of Achilles tendon rupture. The DDD is a standardized dosing unit that represents the average daily dose for an adult for the main indication.[17] The DDD for ofloxacin is 400 mg; for ciprofloxacin, 1000 mg; for norfloxacin, 800 mg; and for nalidixic acid, 4000 mg. We distinguished 3 dosing categories: less than 0.75 DDD (<300 mg of ofloxacin; <750 mg of ciprofloxacin; <600 mg of norfloxacin; <3000 mg of nalidixic acid); 0.75 to 1.25 DDD (300-500 mg of ofloxacin; 750-1250 mg of ciprofloxacin; 600-1000 mg of norfloxacin; 3000-5000 mg of nalidixic acid); and greater than 1.25 DDD (>500 mg of ofloxacin; >1250 mg of ciprofloxacin; >1000 mg of norfloxacin; >5000 mg of nalidixic acid). The prescribed daily dose–DDD ratio is expressed in DDD equivalents and facilitates comparison between drugs but also the estimation of the cumulative exposure to different representatives of one chemical drug class. Duration of use was assessed in currently exposed subjects and defined as the number of days of continuous quinolone therapy.

OTHER RISK FACTORS

Several potential risk factors for Achilles tendon rupture have been reported in the medical literature. These include a history of organ transplantation, end-stage renal failure, hemodialysis, rheumatoid arthritis, osteoarthritis, gout, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, Reiter syndrome, polymyalgia rheumatica, ulcerative colitis, Crohn disease, diabetes mellitus, and systemic corticosteroid use.[18-27] The presence of these risk factors was obtained from the computerized patient records. As an additional potential confounder, we assessed the number of GP visits in the 1.5 years before the index date. Finally, we assessed the indication for treatment with quinolones in the 14 cases and 100 controls who were exposed within 1 month preceding the index date.

ANALYSIS

Relative risks were estimated by odds ratios. Unconditional logistic regression analysis was used to determine the crude and adjusted odds ratios and 95% confidence intervals (CIs) for Achilles tendon rupture within each category of exposure to quinolones, using the nonexposed group as the reference. Similarly, we calculated univariate odds ratios for all other potential risk factors. Subsequently, multivariate logistic regression models were used to adjust for age, sex, use of oral corticosteroids (current, recent, and past exposure), history of musculoskeletal-related disorders, disorders of lipid metabolism, organ transplants or hemodialysis, and the number of GP visits. In these models, we adjusted for all risk factors that were univariately associated in our study with Achilles tendon rupture. In addition, we conducted stratified analyses by age, sex, and concomitant use of corticosteroids to identify potential effect modification, and we tested for statistical interaction. Furthermore, to test whether the GP practice acted as a confounder, we performed conditional logistic regression analyses with matching on GP practice. Population-attributable risk (PAR) proportions were calculated, with the formula

$$PAR = p(OR-1)/[1+p(OR-1)],$$

where OR is the adjusted odds ratio and p, the exposure prevalence. All analyses were conducted using SPSS 9.0 software (SPSS Inc, Chicago, Ill).

RESULTS

We initially identified 1528 potential cases of Achilles tendon rupture during the study period. Of these, 100 patients were excluded by the computer-based algorithms because of the presence of one of the exclusion criteria. After blinded review of the remaining 1428 cases, 61 cases were excluded, 25 because the Achilles tendon rupture was preceded by trauma and 36 because the diagnosis was not compatible with Achilles tendon rup-

Table 1. Characteristics of Cases and Controls*

Characteristic	No. (%)		OR†	95% CI
	Cases (n = 1367)	Controls (n = 50 000)		
Male sex	949 (69.4)	23 986 (48.0)	**2.5**	**2.2-2.8**
Age, y				
Mean	48	47		
18-39	457 (33.4)	20 438 (40.9)	1.0	Reference
40-59	599 (43.8)	16 519 (33.0)	1.6	1.4-1.8
60-79	268 (19.6)	10 429 (20.9)	1.1	1.0-1.3
≥80	43 (3.1)	2614 (5.2)	0.7	0.5-1.0
Calendar year				
1989-1990	22 (1.6)	1265 (2.5)	1.0	Reference
1991-1992	303 (22.2)	11 105 (22.2)	1.6	1.0-2.4
1993-1994	459 (33.6)	16 282 (32.6)	1.6	1.1-2.5
1995-1996	333 (24.4)	13 434 (26.9)	1.4	0.9-2.2
1997-1998	250 (18.3)	7914 (15.8)	1.8	1.2-2.8
GP visits				
Mean	12 (13.8)	14 (39.2)		
0-5	612 (44.8)	23 034 (46.2)	1.0	Reference
6-15	397 (29.0)	15 051 (30.1)	0.99	0.9-1.1
>15	358 (26.2)	11 915 (23.8)	1.1	0.99-1.3
Corticosteroid use	154 (11.3)	2291 (4.6)	**2.6**	**2.2-3.1**
History of musculoskeletal-related disorders	227 (16.6)	6406 (12.8)	**1.4**	**1.2-1.6**
Osteoarthritis	103 (7.5)	3035 (6.1)	**1.3**	**1.0-1.5**
Autoimmune arthritis	95 (6.9)	2833 (5.7)	**1.2**	**1.0-1.5**
Spondyloarthropathies	7 (0.5)	232 (0.5)	1.1	0.5-2.3
Nonarticular rheumatism	19 (1.4)	491 (1.0)	1.4	0.9-2.2
Infectious arthritis	17 (1.2)	376 (0.8)	**1.7**	**1.0-2.7**
Gout	41 (3.0)	742 (1.5)	**2.1**	**1.5-2.8**
Diabetes mellitus	33 (2.4)	1202 (2.4)	1.0	0.7-1.4
Inflammatory bowel disease	6 (0.4)	246 (0.5)	0.9	0.4-2.0
Renal failure	7 (0.5)	173 (0.3)	1.5	0.7-3.2
Transplants/dialysis	3 (0.2)	14 (0.0)	**7.9**	**2.3-27.4**
Disorders of lipid metabolism	35 (2.5)	880 (1.8)	**1.4**	**1.0-2.0**
Obesity	44 (3.2)	1441 (2.9)	1.1	0.8-1.5
Psoriasis	27 (2.0)	1054 (2.1)	0.9	0.6-1.4

Abbreviations: CI, confidence interval; GP, general practitioner; OR, odds ratio.
*Boldface data are statistically significant.
†All odds ratios in this table are unadjusted.

ture (tendinitis, bursitis, and rupture of other tendon). Consequently, 1367 cases were included in our study.

Table 1 shows the demographic and medical characteristics of cases and controls. Of the cases, 69.4% were male and the mean age was 48 years. Kidney transplantation or dialysis, lipid disorders, and systemic corticosteroid use were univariately associated with an increased risk of Achilles tendon rupture. Of the musculoskeletal disorders, osteoarthritis, autoimmune arthritis, and gout were significantly associated with Achilles tendon rupture (Table 1).

To investigate the role of potential confounding cofactors, we studied in the control group of 50 000 subjects which cofactors were univariately associated with quinolone use (**Table 2**). The use of quinolones was significantly lower in men and highest in the elderly. There was a slight increase of quinolone use over the years, and it was strongly associated with the numbers of visits to the GP. Furthermore, persons with a history of musculoskeletal disorders, diabetes mellitus, inflammatory bowel disease, renal failure, and obesity were more frequent users of quinolones (Table 2). In **Table 3**, the associations are given between current use of antibacterial drugs and Achilles tendon rupture. Apart from trimethoprim, also the combination sulfamethoxazole-trimethoprim was associated with a risk increase.

Exposure to any of the quinolones in the 18 months before the index date was observed in 4.5% and 2.0% of the cases and the controls, respectively. The odds ratio for Achilles tendon rupture was 4.3 (95% CI, 2.4-7.8) for current exposure to quinolones, 2.4 (95% CI, 1.5-3.7) for recent exposure, and 1.4 (95% CI, 0.9-2.1) for past exposure, after adjustment for the univariately associated determinants age, sex, corticosteroid use, musculoskeletal disorders, lipid disorders, and transplants or dialysis (**Table 4**). The effect of quinolones on the occurrence of Achilles tendon rupture was not modified by sex, whereas age appeared to be a strong modifier of the effect (test for statistical interaction, $P<.001$). The odds ratio of Achilles tendon rupture was 6.4 (95% CI, 3.0-13.7) in patients aged 60 to 79 years and 20.4 (95% CI, 4.6-90.1) in patients 80 years of age or older, while among patients younger than 60 years there were no cases currently exposed to quinolones (Table 4). As the effect of quinolones seemed more pronounced in elderly people, whereas the exposure was low among younger persons,

Table 2. Characteristics of Users and Nonusers of Quinolones in the Reference Group of 50 000 Individuals*

Characteristic	No. (%)		OR	95% CI
	Quinolone Use	Nonuse		
Male sex	368 (36.1)	23 618 (48.2)	**0.6**	**0.5-0.7**
Age, y				
18-39	267 (26.2)	20 171 (41.2)	1.0	Reference
40-59	317 (31.1)	16 202 (33.1)	**1.5**	**1.3-1.7**
60-79	336 (33.0)	10 093 (20.6)	**2.5**	**2.1-3.0**
≥80	99 (9.7)	2515 (5.1)	**3.0**	**2.4-3.8**
Calendar year				
1989-1990	10 (1.0)	1255 (2.6)	1.0	Reference
1991-1992	175 (17.2)	10 930 (22.3)	2.0	1.0-3.8
1993-1994	380 (37.3)	15 902 (32.5)	3.0	1.6-5.6
1995-1996	262 (25.7)	13 172 (26.9)	2.5	1.3-4.7
1997-1998	192 (18.8)	7722 (15.8)	3.1	1.6-5.9
GP visits				
0-5	83 (8.1)	22 951 (46.9)	1.0	Reference
6-15	294 (28.9)	14 757 (30.1)	**5.5**	**4.3-7.0**
>15	642 (63.0)	11 273 (23.0)	**15.7**	**12.5-19.8**
Corticosteroid use	195 (19.1)	2096 (4.3)	**5.3**	**4.5-6.2**
History of musculoskeletal-related disorders	260 (25.5)	6146 (12.5)	**2.4**	**2.1-2.8**
Osteoarthritis	135 (13.2)	2900 (5.9)	**2.4**	**2.0-2.9**
Autoimmune arthritis	113 (11.1)	2720 (5.6)	**2.1**	**1.7-2.6**
Spondyloarthropathies	10 (1.0)	222 (0.5)	**2.2**	**1.2-4.1**
Nonarticular rheumatism	13 (1.3)	361 (0.7)	1.7	1.0-3.0
Infectious arthritis	21 (2.1)	355 (0.7)	**2.9**	**1.8-1.1**
Gout	19 (1.9)	723 (1.5)	1.3	0.8-2.0
Diabetes mellitus	69 (6.8)	1133 (2.3)	**3.1**	**2.4-3.9**
Inflammatory bowel disease	11 (1.1)	235 (0.5)	**2.3**	**1.2-4.2**
Renal failure	9 (0.9)	164 (0.3)	**2.7**	**1.4-5.2**
Transplants/dialysis	0	14 (0.03)	NA	NA
Disorders of lipid metabolism	26 (2.6)	855 (1.7)	1.5	1.0-2.2
Obesity	62 (6.1)	1379 (2.8)	**2.2**	**1.7-2.9**
Psoriasis	29 (2.8)	1025 (2.1)	1.4	0.9-2.0

Abbreviations: CI, confidence interval; GP, general practitioner; NA, not applicable; OR, odds ratio.
*Boldface data are statistically significant.

Table 3. Current Use of Antibacterial Agents*

Use Variable	No.		Crude OR	95% CI	Adjusted OR	95% CI
	Cases (n = 1367)	Controls (n = 50 000)				
Nonuse of antibacterial drugs	818	30 882	1.0	Reference	1.0	Reference
Past use of antibacterial drugs	264	9841	1.0	0.9-1.2	1.0	0.9-1.2
Recent use of antibacterial drugs	211	7139	1.1	1.0-1.3	1.1	0.9-1.3
Current use of antibacterial drugs†						
Quinolones	12	87	5.2	**2.8-9.6**	**4.0**	**2.1-7.7**
Tetracyclines	12	323	1.4	0.8-2.5	1.3	0.7-2.3
Amoxicillin	15	661	0.9	0.5-1.4	0.8	0.4-1.3
Penicillins	5	164	1.2	0.5-2.8	1.3	0.5-3.3
Amoxicillin and clavulanate potassium	5	144	1.3	0.5-3.2	1.1	0.5-2.9
Trimethoprim and sulfonamides	5	40	4.7	**1.9-12.0**	**3.0**	**1.1-8.3**
Macrolides	8	242	1.2	0.6-2.5	1.1	0.6-2.3
Combined‡	8	144	2.1	1.0-4.3	1.9	0.9-3.9

Abbreviations: CI, confidence interval; OR, odds ratio.
*Boldface data are statistically significant.
†Only antibacterials for which at least 5 cases were exposed.
‡Includes 2 cases and 13 controls exposed to quinolones.

further analyses were conducted only for the subset of patients aged 60 years and older.

Further analyses in this age group showed that the risk of Achilles tendon rupture was strongly dose dependent and increased to a maximum of 12.5 (95% CI, 2.3-68.3) at a dose greater than 1.25 DDD equivalents per day (**Table 5**). A trend analysis was highly significant ($P<.001$). Duration of use of quinolones had little in-

Table 4. Risk of Achilles Tendon Rupture Associated With Quinolones*

Risk Variable	No. Cases (n = 1367)	No. Controls (n = 50 000)	Crude OR	Adjusted OR†	95% CI
Quinolone use					
None	1305	48 981	1.0	1.0	Reference
Current use (0-1 mo)	14	100	**5.3**	**4.3**	**2.4-7.8**
Recent use (2-6 mo)	24	314	**2.9**	**2.4**	**1.5-3.7**
Past use (7-18 mo)	24	605	1.5	1.4	0.9-2.1
Age <60 y					
No quinolone exposure	1029	36 373	1.0	1.0	Reference
Current quinolone exposure	0	50	NA	NA	NA
Recent quinolone exposure	10	172	2.1	1.8	1.0-3.5
Past quinolone exposure	17	362	1.7	1.6	1.0-2.7
Age 60-79 y					
No quinolone exposure	243	10 093	1.0	1.0	Reference
Current quinolone exposure	11	41	**11.1**	**6.4**	**3.0-13.7**
Recent quinolone exposure	9	113	3.3	2.0	1.0-4.2
Past quinolone exposure	5	182	1.1	0.8	0.3-2.0
Age ≥80 y					
No quinolone exposure	33	2515	1.0	1.0	Reference
Current quinolone exposure	3	9	**25.4**	**20.4**	**4.6-90.1**
Recent quinolone exposure	5	29	**13.1**	**7.4**	**2.4-22.9**
Past quinolone exposure	2	61	2.5	2.8	0.6-12.6

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Boldface data are statistically significant.
†Adjusted for age, sex, corticosteroid use, musculoskeletal-related disorders, disorders of lipid metabolism, and transplants or dialysis.

Table 5. Risk of Achilles Tendon Rupture Associated With Individual Quinolones and According to Dose Among Patients 60 Years and Older*

Risk Variable	No. Cases	No. Controls	Crude OR	Adjusted OR†	95% CI
Quinolones					
None	276	12 608	1.0	1.0	Reference
Ofloxacin	5	5	**45.7**	**28.4**	**7.0-115.3**
Ciprofloxacin	6	40	**6.9**	**3.6**	**1.4-9.1**
Norfloxacin	1	5	**9.1**	**14.2**	**1.6-128.6**
Nalidixic acid	2	0	NA	NA	NA
Prescribed daily dose‡					
None	276	12 608	1.0	1.0	Reference
0.01-0.75 DDD_{eqs}	6	99	**2.8**	1.7	0.7-4.1
0.76-1.25 DDD_{eqs}	19	90	**9.6**	**6.7**	**3.8-11.7**
>1.25 DDD_{eqs}	3	3	**45.7**	**12.5**	**2.3-68.3**

Abbreviations: CI, confidence interval; DDD_{eqs}, defined daily dose equivalents; NA, not applicable; OR, odds ratio.
*Boldface data are statistically significant.
†Adjusted for age, sex, corticosteroid use, musculoskeletal-related disorders, disorders of lipid metabolism, and transplants or dialysis.
‡Prescribed daily dose of quinolones within 3 months preceding the index date.

fluence on the risk of Achilles tendon rupture, since almost all courses were given for similar short periods. Most courses of quinolones were given for respiratory tract or urinary tract infections. There was no significant difference in indications between cases and controls (respiratory vs urinary tract infections, $P=.17$; respiratory tract vs other infections, $P=.20$; urinary tract vs other infections, $P=.77$), which demonstrated that confounding by indication is unlikely. The odds ratio of Achilles tendon rupture was 28.4 (95% CI, 7.0-115.3) for current exposure to ofloxacin, while the odds ratios were 3.6 (95% CI, 1.4-9.1) and 14.2 (95% CI, 1.6-128.6) for ciprofloxacin and norfloxacin, respectively (Table 5). Concomitant use of quinolones with oral corticosteroids modified the risk of Achilles tendon rupture (test for statistical interaction, $P<.001$). The odds ratio of Achilles tendon disorders associated with current exposure to quinolones was 5.3 (95% CI, 1.8-15.2) in patients not using oral corticosteroids, and 17.5 (95% CI, 5.0-60.9) and 18.4 (95% CI, 1.4-240.2) in patients with current and recent exposure to oral corticosteroids, respectively (**Table 6**). As parenteral corticosteroids are often used to treat tendinitis, we excluded these from the analyses. Analyses with conditional logistic regression analyses with match-

Table 6. Current Quinolone Exposure Among Patients 60 Years and Older Stratified for Concurrent Exposure to Oral Corticosteroids*

Exposure Variable	No.		Crude OR	Adjusted OR†	95% CI
	Cases	Controls			
No oral corticosteroids					
No quinolone exposure	228	11 877	1.0	1.0	Reference
Current quinolone exposure	4	39	**5.3**	**5.3**	**1.8-15.2**
Current exposure to oral corticosteroids					
No quinolone exposure	24	194	1.0	1.0	Reference
Current quinolone exposure	9	5	**14.6**	**17.5**	**5.0-60.9**
Recent exposure to oral corticosteroids					
No quinolone exposure	14	263	1.0	1.0	Reference
Current quinolone exposure	1	2	9.4	**18.4**	**1.4-240.2**
Past exposure to oral corticosteroids					
No quinolone exposure	10	274	1.0	1.0	Reference
Current quinolone exposure	0	4	NA	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Boldface data are statistically significant.
†Adjusted for age, sex, musculoskeletal-related disorders, disorders of lipid metabolism, and transplants or dialysis.

ing on GP practice gave similar results but lower precision (data not shown).

The absolute overall risk of Achilles tendon ruptures was 5.5 and 3.5 per 100 000 person-years in people aged 60 to 79 years and 80 years or older, respectively. Given the population-attributable risk percentage of 2.2% in patients aged 60 to 79 years and of 6.3% in people 80 years or older, these figures mean that the absolute risk of Achilles tendon ruptures is low, even in those 80 years or older.

COMMENT

Rupture of the Achilles tendon is a serious condition that may lead to significant morbidity and often requires surgical treatment. In our study, use of quinolones was independently associated with an increased risk of Achilles tendon rupture. This effect was demonstrated only in persons aged 60 years or older, and within this group concomitant use of corticosteroids increased the risk substantially. These findings confirm the results from case series, case reports, and one case-control study that suggested that age greater than 60 years and concurrent corticosteroid use were risk factors for quinolone-induced tendon disorders.[6,9,28,29]

Among the individual quinolones, the highest risk of Achilles tendon rupture was found for users of ofloxacin. Although the CIs of the risk estimates overlapped those of the other quinolones, this finding is consistent with data from previous studies,[30] case series,[6] case reports,[7,8] and animal toxicity testing,[31] which showed that ofloxacin and pefloxacin (which is not marketed in the United Kingdom) were associated with a higher risk of tendon disorders than other quinolones.

In our study, oral corticosteroid use was not only an important independent risk factor but, in combination with current exposure to quinolones, also strongly increased the risk of Achilles tendon rupture in patients older than 60 years. Other independent risk factors for Achilles tendon rupture were osteoarthrosis, inflammatory joint diseases, and gout. Furthermore, patients who received dialysis or who underwent a renal transplant were at higher risk of developing Achilles tendon rupture, which is consistent with the literature.[18,19,21,24,27] Adjustment for these risk factors, however, did not change the risk estimate for quinolones considerably.

The incidence of Achilles tendon rupture varies among different studies but seems to have increased in the past few decades and shows a bimodal age distribution.[32,33] The first peak incidence occurs between 30 and 40 years of age. These tendon ruptures are mostly because of sport activity. The second peak occurs between 70 and 80 years of age, and these tendon ruptures are mostly not sport related.[32,33] Data about the incidence of quinolone-associated Achilles tendon rupture is scarce. In a study with prescription event monitoring, the incidence of tendon rupture was estimated as 2.7 per 10 000 patients for ofloxacin and 0.9 per 10 000 patients for ciprofloxacin.[34]

The most important risk factor for the development of Achilles tendon rupture is probably sporting, in particular the recreational sports that demand sudden acceleration and jumping.[26,27,35] In our study, we could not get information about sporting activity, but this may not have confounded the results since all patients with an Achilles tendon rupture who were currently exposed to quinolones were 60 years of age or older, whereas the incidence of sport-related ruptures is highest between 30 and 40 years of age and that of non–sport-related ruptures peaks between 50 and 70 years of age.[32,33]

The mechanism of Achilles tendon rupture induced by quinolones is not well understood, although it is known that quinolones exhibit a pronounced affinity for connective tissues. A Japanese group succeeded in producing quinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin, but not in adult rats.[31,36] Others succeeded in providing experimental evidence of pefloxacin-induced oxidative stress in the Achilles tendon that altered proteoglycan anabolism and oxidized collagen.[37] Recently, it was hypothesized that quinolones may exert their effect by disturbing the physiologic interaction between cells and matrix by chelating divalent ions.[38]

Some potential limitations should be considered in the interpretation of our results. Selection bias is unlikely, since our study was population based and cases of Achilles tendon rupture will ultimately come to the attention of the GP. Controls were randomly selected from the study base, and the index dates were also randomly assigned. We cannot exclude the possibility that some of the Achilles tendon ruptures were misclassified despite extensive review of the computerized patient records. As the review was blinded to exposure to quinolones, however, any misclassification was unbiased and thus would lead to a conservative estimate rather than to an overestimation of the risk of Achilles tendon rupture due to quinolones. Prescription data in the General Practice Research Database are automatically registered when the GP writes a prescription. These data are considered complete, which means that misclassification of quinolone use was unlikely. Recall bias can be excluded, since data on drug use were recorded before the onset of disease. During the 1990s, there has been an increase in case reports implicating that quinolones may cause tendon disorders. As a consequence, diagnostic suspicion bias might partly explain the observed increase in relative risk, if physicians diagnose Achilles tendon disorders more readily in patients currently using quinolones. However, adjustment for calendar year did not change the relative risk, so we assume that diagnostic bias did not play a major role. Confounding by indication is unlikely, since none of the indications for use of quinolones are known risk factors for Achilles tendon rupture, and adjustment for potential risk factors such as history of musculoskeletal disorders, gout, lipid disorders, and kidney transplantation did not change the estimate considerably.

In conclusion, our data confirm that exposure to quinolones increases the risk of Achilles tendon disorders, in particular in elderly patients who concomitantly use oral corticosteroids. Calculation of the population-attributable risk among the elderly suggests that approximately 2% to 6% of all Achilles tendon ruptures in people older than 60 years can be attributed to the use of quinolones. Given the low incidence of Achilles tendon rupture, these absolute risks are modest. Nevertheless, prescribers should be aware of this risk and try to avoid the combination with oral corticosteroids, or should prescribe alternative antimicrobial agents if possible.

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