

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/6471518>

# Use of fluroquinolone and risk of Achilles tendon rupture: A population-based cohort study

ARTICLE *in* EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY · JUNE 2007

Impact Factor: 2.97 · DOI: 10.1007/s00228-007-0265-9 · Source: PubMed

---

CITATIONS

26

---

READS

66

## 4 AUTHORS, INCLUDING:



Jacob Sode

Statens Serum Institut

10 PUBLICATIONS 50 CITATIONS

SEE PROFILE



Jesper Hallas

University of Southern Denmark

270 PUBLICATIONS 5,600 CITATIONS

SEE PROFILE



Annmarie Lassen

University of Southern Denmark

55 PUBLICATIONS 1,079 CITATIONS

SEE PROFILE

# Use of fluoroquinolone and risk of Achilles tendon rupture: a population-based cohort study

Jacob Sode · Niels Obel · Jesper Hallas ·  
Annmarie Lassen

Received: 7 November 2006 / Accepted: 9 January 2007 / Published online: 3 March 2007

© Springer-Verlag 2007

## Abstract

**Objective** Several case-control studies have reported that the use of fluoroquinolone increases the risk of rupture of the Achilles tendon. Our aim was to estimate this risk by means of a population-based cohort approach.

**Setting** Data on Achilles tendon ruptures and fluoroquinolone use were retrieved from three population-based databases that include information on residents of Funen County (population: 470,000) in primary and secondary care during the period 1991–1999. A study cohort of all 28,262 first-time users of fluoroquinolone and all incident cases of Achilles tendon ruptures were identified.

**Main outcome measures** The incidence rate of Achilles tendon ruptures among users and non-users of fluoroquinolones and the standardised incidence rate ratio associating fluoroquinolone use with Achilles tendon rupture were the main outcome measures.

**Results** Between 1991 and 2002 the incidence of Achilles tendon rupture increased from 22.1 to 32.6/100,000 person-years. Between 1991 and 1999 the incidence of fluoroquinolone users was 722/100,000 person-years, with no apparent trend over time. Within 90 days of their first use of fluoroquinolone, five individuals had a rupture of the

Achilles tendon; the expected number was 1.6, yielding an age- and sex-standardised incidence ratio of 3.1 [(95% confidence interval (95%CI): 1.0–7.3). The 90-day cumulative incidence of Achilles tendon ruptures among fluoroquinolone users was 17.7/100,000 (95%CI: 5.7–41.3), which is an increase of 12.0/100,000 (95%CI: 0.0–35.6) compared to the background population.

**Conclusion** Fluoroquinolone use triples the risk of Achilles tendon rupture, but the incidence among users is low.

**Keywords** Achilles tendon · Antibiotics · Cohort study · Incidence · Quinolone

## Abbreviations

CI confidence interval

## Introduction

Achilles tendon rupture is a condition that manifests as complete or partial rupture of the Achilles tendon. It is mainly related to physical activity, although rheumatoid arthritis and the use of corticosteroids are additional risk factors [1, 2]. The prevalence of Achilles tendon rupture has been reported in a number of studies, with a range of 6 to 37/100,000 person-years, and it seems to increase with calendar time [2–7]. Although most young individuals recover completely following an Achilles tendon rupture, the condition is associated with considerable morbidity and loss of function among elderly [8, 9].

Population-based cohort and case-control studies have demonstrated that fluoroquinolones can increase the risk of tendinitis or Achilles tendon ruptures by a factor of three to six [10–12]. The risk of Achilles tendon rupture

---

Grant support: there is no funding.

---

J. Sode · N. Obel · A. Lassen (✉)  
Department of Infectious Medicine, Odense University Hospital,  
5000 Odense C, Denmark  
e-mail: Annmarie.lassen@ouh.fyns-amt.dk

J. Hallas  
Clinical Pharmacology, Institute of Clinical Pharmacology,  
University of Southern Denmark,  
Odense, Denmark

is higher among the elderly than among young fluoroquinolone users [8, 10–12]. In two population-based studies, the absolute risk of Achilles tendon diseases among patients who use fluoroquinolones was found to range between 7.74/100,000 days at risk and 3.2/1000 patient-years [10, 12].

The mechanisms behind the fluoroquinolone effect is unknown, but it is probably due to direct toxicity and degenerative changes on collagen fibres [2, 8, 9]. Fluoroquinolones possess chelating properties that are likely involved in tendon toxicity as animals fed a magnesium-deficient diet are at increased risk of fluoroquinolone-induced tendon disorders [13, 14].

The aim of the present study was to describe the absolute and relative incidence rate of Achilles tendon rupture among fluoroquinolone-treated patients in comparison to that in the general population.

## Methods

We retrieved data from three large population-based registers: the Patient Administrative System of Funen County, the Odense University Pharmacoepidemiological Database and the Civil Registration System. Data were linked by the personal identifying code that is unique for each Danish citizen [15].

Since 1974, the Patient Registration System of the County of Funen has included 100% of all in-hospital contacts in Funen County; in 1989, this was expanded to include all out-patient visits as well. We retrieved data on all discharges with a diagnosis code of Achilles tendon rupture for the period 1974–2002 (ICD 8: 90810 and ICD 10: S860).

Since 1990, prescriptions reimbursed in Funen County have been registered in the Odense Pharmacoepidemiological Database [16]. Data have been complete since 1992. Each record contains the date of purchase, a full account of what has been dispensed and the unique personal registration number. Prescriptions for fluoroquinolone have been exempted from reimbursement since May 17, 1999, after which time they were also no longer included in the database. We retrieved data on all prescriptions for fluoroquinolones, tetracyclines, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides and glycopeptides between January 1, 1991 and May 17, 1999.

To assess any misclassification of cases, we manually reviewed the clinical records of all Achilles tendon ruptures identified among users of fluoroquinolone and found no misclassified case out of five registered Achilles tendon ruptures. Data on death and migration out of the county for all subjects were obtained from the Danish Civil Registration System.

## Analyses

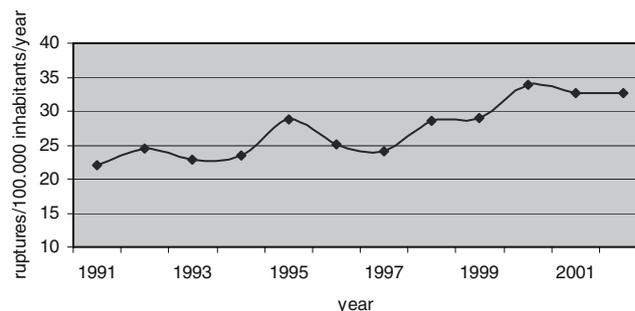
All patients registered for an Achilles tendon rupture between 1974 and 2002 were identified, and the age- (10-year age groups) and gender-specific incidence of Achilles tendon rupture between 1991 and 2002 was calculated.

All redeemed prescriptions of fluoroquinolone between January 1, 1991 and May 17, 1999 were identified; for comparison purposes, we also identified all other redeemed prescriptions for all other antibiotics in this same period. Patients were excluded if they were not a resident of Funen County at the time of the Achilles tendon rupture and/or at the time of the redeemed prescription.

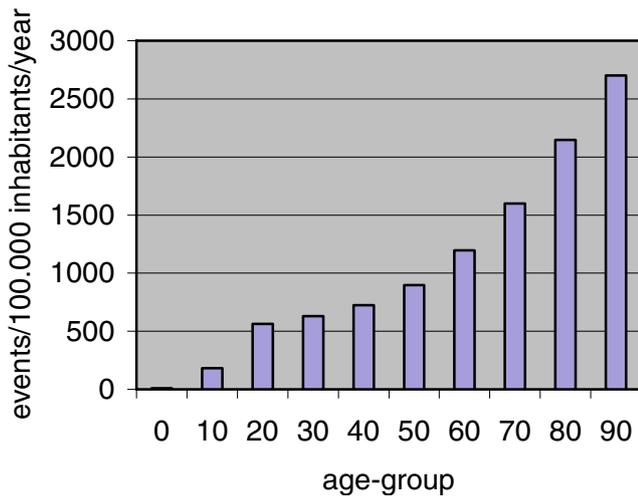
A cohort of all patients with first redeemed prescriptions on fluoroquinolones was identified. We assigned a 90-day risk window to each prescription. Relative risk was calculated as the ratio between the observed and the expected case numbers for fluoroquinolone users (standardised incidence ratio by indirect standardisation). The absolute risk was expressed as the 90-day cumulative incidence proportion per 100,000 persons. This measure was calculated for new fluoroquinolone users and for the background population, and the difference was termed the risk difference. We standardised for gender and for age in 10-year intervals in all comparisons. Ninety-five percent confidence intervals (95%CI) were calculated under the assumption of a Poisson distribution for the number of cases among fluoroquinolone users.

We calculated the population attributable proportion using standard techniques [17]. This measure expresses the proportion of all Achilles tendon ruptures cases that are caused by fluoroquinolone intake.

With the aim of controlling for confounders that are stable over time, a case-crossover analysis was performed [18]. All patients with a first-time rupture of the Achilles tendon between July 1, 1992 and May 17, 1999 were identified and subsequently given two dates: a case-date, which was the date that the Achilles tendon rupture was registered, and a control-date, which was the date 365 days before the case-date. Redeemed prescriptions of fluoroquinolone 90 days before the case- and control-date, respec-



**Fig. 1** Incidence rate of Achilles tendon rupture in Funen County in the period 1991–2002 (cases/100,000 persons per year)



**Fig. 2** Age-specific incidence of fluoroquinolone use in Funen County between 1991 and 1999

tively, were retrieved. The odds ratio (OR) was calculated by conventional techniques as the discordant exposure ratio [18]. In this analysis, only subjects who were resident in Funen County for at least 18 months were included. We also included all uses of fluoroquinolones – not only first use as in the main analysis. The reason for the more comprehensive definition of usage was based on the fact that if we included only the first use of fluoroquinolone, subjects could not possibly be concordant users both on the index date and on the reference date and, therefore, the conditions for performing a case-crossover study would not be met.

All analyses were repeated for other antibiotics as a group (tetracyclines, chloramphenicols, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides and glycopeptides).

Analyses were performed using STATA (release 8; Stata Corp, College Station, Tex.). Approval was obtained from the Danish Data Protection Board. Approval from an ethics committee was not required.

**Results**

Between 1991 and 2002 a total of 1538 patients had an incident involving the rupture of the Achilles tendon. The

mean age of the patient at the time of the rupture was 44.2 years, and 75% were men. The mean incidence rate was 27.3/100,000 person-years, but there was a trend towards an increased incidence during this period – from 22.1/100,000 person-years in 1991 to 32.6/100,000 person-years in 2002 (Fig. 1). The peak incidence rate was found among persons aged 30–49 years (55/100,000 persons per year).

Between January 1, 1991 and May 17, 1999, we identified a total of 28,262 patients with a first episode of fluoroquinolone use. The mean age of these patients was 55 years (SD: 20.4), and 62% were women. The incidence of first fluoroquinolone use varied between 500/100,000 persons per years in 1997 and 987/100,000 persons per year in 1994, with no stable time-trend, and with a mean of 722/100,000 persons per year. The incidence was strongly related to age, with an incidence of 182/100,000 persons per year for the 10- to 19-year-old group, increasing to 2146/100,000 persons per year for the 80- to 89-year-old group (Fig. 2).

Among the 28,262 persons who had redeemed a prescription on fluoroquinolone for the first time, five had an Achilles tendon rupture during the first 90 days of follow-up; the expected number was 1.6, and the standardised incidence rate ratio 3.1 (95%CI: 1.0–7.3) (Table 1). The absolute 90-day risk was 17.7/100,000 persons, and the absolute risk difference when compared to the general population was 12.0/100,000 persons per 90-day period (Table 2).

Among those patients ≥60 years the standardised incidence ratio was 4.0 (95%CI: 0.5–14.4) in the 90-day time-window, while the standardised incidence ratio was 2.5 (95%CI: 0.5–7.4) for patients younger than 60 years (Table 1). The corresponding population attributable proportions are 0.3, 0.2 and 1.2% for the entire population, for persons <60 years of age and for persons ≥60 years of age, respectively.

A total of 911 patients had a first-time Achilles tendon rupture between July 1, 1992 and May 17, 1999. Nine of these had used fluoroquinolone in the 90-day period immediately preceding the Achilles tendon rupture (case-date). One year previously, five individuals had used

**Table 1** Observations of Achilles tendon ruptures within 90 days of the first-time use of fluoroquinolone and other antibiotics

Antibiotic use in relation to age category	Observed Achilles tendon ruptures (n)	Expected Achilles tendon ruptures (n)	Standardised incidence ratio <sup>a</sup> (95% confidence interval)
Antibiotic Fluoroquinolone use	5	1.6	3.1 (1.0–7.3)
Age <60 years	3	1.2	2.5 (0.5–7.4)
Age ≥60 years	2	0.5	4 (0.5–14.4)
Other antibiotic use	21	25.5	0.8 (0.5–1.3)
Age <60 years	15	21.8	0.7 (0.4–1.1)
Age ≥60 years	6	3.7	1.6 (0.6–3.5)

<sup>a</sup> The standardised incidence rate ratio is calculated by indirect standardisation using incidence data from the background population

**Table 2** Absolute risk and incidence rate difference for Achilles tendon rupture within 90 days of the first-time use of fluoroquinolone or other antibiotics

Antibiotic	First-time users ( <i>n</i> )	Observed Achilles tendon ruptures ( <i>n</i> )	<i>n</i> / 100,000 per period (95% CI)	Risk difference to background population <i>n</i> /100,000 per period (95% CI)
Fluoroquinolone	28,262	5	17.7 (5.7–41.3)	12.0 (0.0–35.6)
Other antibiotic	401,080	21	5.2 (3.2–8.0)	–1.0 (–2.9–1.8)

Abbreviations: CI, Confidence interval

fluoroquinolone in the 90 days immediately preceding the control date. One patient had used fluoroquinolones on both occasions. This yields an OR of 1.8 (95%CI, 0.5–6.9) for a 90-day exposure window (Table 3).

Among the 401,080 persons who had redeemed prescriptions on other antibiotics for the first time, 21 had a rupture of the Achilles tendon during the first 90 days of follow-up; the expected number was 25.5, and the standardised incidence ratio was 0.8 (95% CI 0.5–1.3) (Table 1). The 90-day risk was 5.2/100,000 persons, and the risk difference was 1.0/100,000 persons per 90-day period (Table 2).

Of the 911 patients with a first-time Achilles tendon rupture between July 1, 1992 and May 17, 1999, 83 had used other antibiotics during the 90 days immediately preceding the Achilles tendon rupture (case-date). One year previous, 93 had used other antibiotics during the 90 days immediately preceding the control-date, yielding an OR of 0.9 (95%CI: 0.6–1.2) in the case-crossover analysis (Table 3).

## Discussion

The results of this study indicate that the risk of a person suffering a rupture of the Achilles tendon was threefold higher within 90 days of using fluoroquinolone for the first time than that calculated for the background population. In addition, we found that the absolute risk of Achilles tendon rupture is low.

The strength of the study is its population-based cohort design. More than 95% of all hospital treatments are performed within the public health system, and since contacts are registered by the Danish personal registration numbers, we were able to follow individual persons over

**Table 3** Case-crossover analysis of prescriptions on fluoroquinolone/ other antibiotics in the different time windows for 911 patients with an incident Achilles tendon rupture

Antibiotic	Index date	Reference date <sup>a</sup>	Odds ratio (95%CI)
Fluoroquinolone	9	5	1.8 (0.5–6.9)
Other antibiotic	83	93	0.9 (0.6–1.2)

<sup>a</sup> We used a reference time of 365 days before the index date

time with nearly no loss to follow-up. However, a main weakness of the study is that although we were able to identify a study cohort of 28,262 individuals who were first-time users of fluoroquinolone, only five of these had a rupture of the Achilles tendon during the first 90 days of follow-up. Another weakness of our study is the risk of misclassified cases of Achilles tendon rupture among non-users of fluoroquinolone. To decrease this risk, we reviewed the records of all Achilles tendon ruptures among fluoroquinolone users and found no misclassified case. No validation has been undertaken for the non-users, which may have biased our relative risk measures and our risk difference towards lower values. A further weakness is the fact that although we have information on the total doses of retrieved fluoroquinolone, we have no information on the prescribed daily dose, which may result in misclassification of the usage period. However, as yet it is unknown if the risk of Achilles tendon rupture is associated to the actual use of fluoroquinolone or if it is a long-term effect following its use. We chose a 90-day period for the main results and repeated the analysis with the risk of Achilles tendon rupture in different time-windows following redemption of the first prescription of fluoroquinolone. The relative risk was 3.6 in a 30-day window and 2.7 in a 180-day window, which supports an assumption of a long-term effect.

Between 1991 and 2002 the incidence of Achilles tendon ruptures increased from 22.1 to 32.6/100,000 persons per year in Funen County. The level – as well as the time-related increasing incidence – are in accordance with results from previous studies [2–7]. The observed incidence of fluoroquinolone users was 722/100,000 persons per year with no increasing trend with time but with a much higher use among the elderly than among young persons. No other incidence figures exists, but in The Netherlands the prevalence of fluoroquinolone users increased from 840/100,000 inhabitants per year in 1991 to 2040/100,000 inhabitants per year in 1996 [19]. In Funen County, the prevalent use of fluoroquinolone started to increase after 2003, and in 2005 the number of prevalent users was 1100/100,000 persons (<http://www.medstat.dk/MedStatDataViewer.php>; accessed July 2006).

Among patients younger than 60 years of age, we found that the risk of Achilles tendon rupture was 2.5-fold higher

among fluoroquinolone users than in the general population and that the proportion of Achilles tendon ruptures related to the use of fluoroquinolone was less than 1%. Among patients >60 years the relative risk was fourfold higher. These results are consistent with results from a study of Van der Linden, who demonstrated that there was no increased relative risk for patients under 60 years of age but that there was a 6.4-fold increased relative risk for patients aged 60–79 years and a 20.4-fold increased relative risk for patients aged 80 years or more [11]. Van der Linden estimated that 2–6% of all Achilles tendon ruptures among patients older than 60 years could be attributed to the use of fluoroquinolone [11]. The apparent discrepancy with our figures is probably best explained by local antibiotic policy; the Danish tradition for antibiotic use is extremely conservative, with low use in general and narrow-spectrum penicillins as the preferred choice [20]. Thus, in the Danish setting, Achilles tendon ruptures would only rarely be explained by fluoroquinolone use. The reason for the observed age-related difference in relative risk is unknown, but it may be related to an age-specific effect of fluoroquinolone, comorbidity or concomitant use of corticosteroids [8].

We controlled for possible confounding factors as age and sex but were unable to control for other factors, such as physical activity, comorbidity and the use of corticosteroids; this inability is an important weakness of the analysis. To compensate – partially – for the confounding factors of chronic comorbidity and average physical activity, we performed a case-crossover analysis of patients with first time Achilles tendon ruptures. Although our results did not reach statistical significance, the analysis supports the observation of an increased risk of Achilles tendon rupture among patients who use fluoroquinolone. However, all our results have to be interpreted with caution as we have made no direct control for other confounding factors than age and sex.

With the aim of demonstrating that the observed effect was related to a specific effect of fluoroquinolone, we repeated the analysis in patients treated with non-quinolone antibiotics and found no increased risk of Achilles tendon rupture among these patients. This supports our hypothesis that the increased risk of Achilles tendon ruptures seen among fluoroquinolone-treated patients is related to the drug rather than its indication.

In conclusion, we found that although the relative risk of Achilles tendon rupture is increased by a factor three among patients who use fluoroquinolones, the absolute increase in risk is low – only 12 per 100,000 treated. This corresponds to only one excess Achilles tendon rupture per 8300 treatments and should not be a factor determining whether or not to

prescribe fluoroquinolones to patients with serious infections, for whom this antibiotic is appropriate.

## References

- Jarvinen TA, Kannus P, Paavola M et al (2001) Achilles tendon injuries. *Curr Opin Rheumatol* 13(2):150–155
- Jarvinen TA, Kannus P, Maffulli N et al (2005) Achilles tendon disorders: etiology and epidemiology. *Foot Ankle Clin* 10(2):255–266
- Leppilähti J, Puranen J, Orava S (1996) Incidence of Achilles tendon rupture. *Acta Orthop Scand* 67(3):277–279
- Maffulli N, Waterston SW, Squair J et al (1999) Changing incidence of Achilles tendon rupture in Scotland: a 15-year study. *Clin J Sport Med* 9(3):157–160
- Houshian S, Tscherning T, Riegels-Nielsen P (1998) The epidemiology of Achilles tendon rupture in a Danish county. *Injury* 29(9):651–654
- Levi N (1997) The incidence of Achilles tendon rupture in Copenhagen. *Injury* 28(4):311–313
- Suchak AA, Bostick G, Reid D et al (2005) The incidence of Achilles tendon ruptures in Edmonton, Canada. *Foot Ankle Int* 26(11):932–936
- Melhus A (2005) Fluoroquinolones and tendon disorders. *Expert Opin Drug Saf* 4(2):299–309
- Khaliq Y, Zhanel GG (2003) Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 36(11):1404–1410
- van der Linden PD, Sturkenboom MC, Herings RM et al (2002) Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ* 324(7349):1306–1307
- van der Linden PD, Sturkenboom MC, Herings RM et al (2003) Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 163(15):1801–1807
- van der Linden PD, van de LJ, Nab HW et al (1999) Achilles tendinitis associated with fluoroquinolones. *Br J Clin Pharmacol* 48(3):433–437
- Shakibaei M, Pfister K, Schwabe R et al (2000) Ultrastructure of Achilles tendons of rats treated with ofloxacin and fed a normal or magnesium-deficient diet. *Antimicrob Agents Chemother* 44(2):261–266
- Shakibaei M, de Souza P, van Sickle D et al (2001) Biochemical changes in Achilles tendon from juvenile dogs after treatment with ciprofloxacin or feeding a magnesium-deficient diet. *Arch Toxicol* 75(6):369–374
- Frank L (2000) Epidemiology. When an entire country is a cohort. *Science* 287(5462):2398–2399
- Gaist D, Sorensen HT, Hallas J (1997) The Danish prescription registries. *Dan Med Bull* 44(4):445–448
- Rotmann KJ (2006) *Epidemiology – an introduction*. Oxford Press, Oxford
- Maclure M (1991) The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 133(2):144–153
- van der Linden PD, Nab HW, Simonian S et al (2001) Fluoroquinolone use and the change in incidence of tendon ruptures in the Netherlands. *Pharm World Sci* 23(3):89–92
- Goossens H, Ferech M, Vander SR et al (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 365(9459):579–587