FLUOROQUINOLONES AND TENDON DISORDERS

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van der Linden PD, Herings RMC, Sturkenboom MCJM, Nab HW, Simonian S, Leufkens HGM, Stricker BHCh. Utilisation of fluoroquinolones in the Netherlands; comparison to other countries. (Submitted).

Chapter 3
van der Linden PD, Feenstra J, in 't Veld BA, van Puijenbroek EP, Herings RMC, Leufkens HGM, Stricker BHCh. Tendon disorders attributed to fluoroquinolones; a study on 42 spontaneous reports in the period 1988 to 1998. (Arthritis Rheum, accepted for publication).

Chapter 4
van der Linden PD, Nab HW, Simonian S, Stricker BHCh, Leufkens HGM, Herings RMC. Fluoroquinolone use and the change in incidence of tendon ruptures in the Netherlands. (Pharm World Sci, accepted for publication).

Chapter 5
van der Linden PD, van de Lei J, Nab HW, Knol A, Stricker BHCh. Achilles tendinitis associated with fluoroquinolones. Br J Clin Pharmacol 1999; 48:433-7.

Chapter 6
van der Linden PD, Sturkenboom MCJM, Herings RMC, Leufkens HGM, Stricker BHCh. Fluoroquinolones and the risk of Achilles tendon disorders. (Submitted).

Chapter 7
van der Linden PD, Sturkenboom MCJM, Herings RMC, Leufkens HMG, Stricker BHCh. Fluoroquinolones increase the risk of Achilles tendon rupture, especially in elderly patients on oral corticosteroids. (Submitted).

CHAPTER 1

INTRODUCTION

Since the 'thalidomide disaster' in 1961, there is extensive national and international legislation for the registration and monitoring of drugs. The current drug approval process in most developed countries includes pre-clinical animal testing followed by three phases of clinical testing during which the efficacy and safety of drugs are determined (1). Despite this process, however, not all drug effects are known at the moment of marketing approval (2). For most indications less than 3,000 patients are exposed to a drug during the pre-registration phase. This implies that an adverse reaction can only be detected with 95% certainty if the occurrence is at least 1 per 1,000 patients and the background incidence is zero (3). After regulatory approval, however, millions of people will use the drug with the possibility that less common unknown adverse drug reactions can emerge. In order to enable continuous reassessment of the benefit/risk ratio of a specific drug in the post-marketing phase, it is necessary to continuously monitor utilisation and effects of drugs after their approval.

In 1984, Lawson first introduced the term pharmaco-epidemiology as a bridge between clinical pharmacology and epidemiology (4). Clinical pharmacology is the study of the effects of drugs in humans (5), while epidemiology is the study of the distribution and determinants of disease frequency in human populations (6). Similarly, the definition of pharmaco-epidemiology is the study of the distribution and determinants of disease frequency with the drug as the main determinant of interest (1, 7). Pharmaco-epidemiology borrows its focus of research from clinical pharmacology and its research methods from epidemiology. The study designs that can be applied vary from case reports to large observational case-control or cohort studies, or sometimes postmarketing clinical trials. Pharmaco-epidemiology can provide qualitative as well as quantitative information on both the beneficial and harmful effects of drugs during use under everyday circumstances and is important for the assessment of the benefit/risk ratio of that particular drug in a naturalistic setting.

In this thesis, we focus on a relatively uncommon adverse reaction to fluoroquinolones, namely the association between fluoroquinolone use and the occurrence of tendon disorders. Fluoroquinolones are antibacterial agents which are chemically related to nalidixic acid and act by inhibiting bacterial DNA gyrase (topoisomerase II) (8). Nalidixic acid is a 1,8-naphtyridine molecular structure that was identified by Lesher and associates in 1962 among the by-products of chloroquine synthesis (9). In the eighties the first representatives of the fluoroquinolone antimicrobial agents, such as ofloxacin, norfloxacin, ciprofloxacin, and pefloxacin, were introduced in clinical practice (Figure 1). All

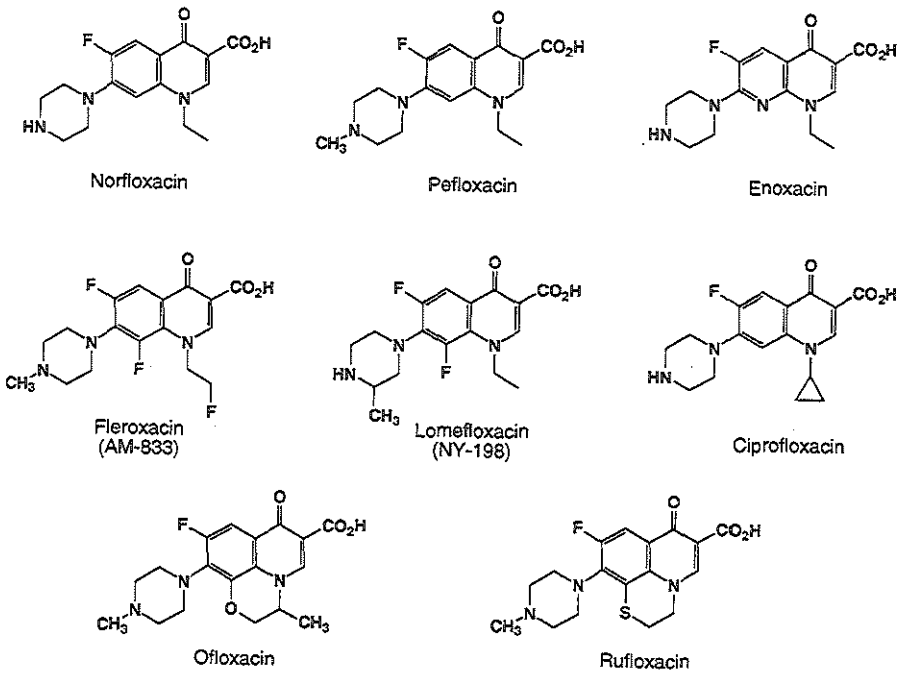

Figure 1
Fluoroquinolones

fluoroquinolones have a fluor-atom at the 6th position of the ring structure. Today the fluoroquinolones are among the most frequently prescribed antibacterial agents. The recent approval of fluoroquinolones with a broader antibacterial spectrum and the possibility of once daily dosing may lead to an even more frequent use of these drugs in the future (10).

Fluoroquinolones have good pharmacokinetic properties, bactericidal action at low minimal inhibitory concentration, and a broad antimicrobial spectrum (11). The oral bioavailability exceeds 50 percent and for several agents approaches even 100 percent. Food does not substantially reduce the absorption of fluoroquinolones but it may delay the time to reach peak concentration. Tissue penetration is high and concentrations in urine, kidney tissue, prostate tissue, stool, bile, lung, neutrophils, and macrophages may exceed serum concentrations (9). Fluoroquinolones are active against a large spectrum of gram-negative and gram-positive organisms, as well as against some anaerobic bacteria (12). As such they are indicated for the treatment of a wide variety of infectious diseases, including urinary tract infections, prostatitis, sexually transmitted diseases,

respiratory tract infections, gastrointestinal and abdominal infections, and bone and joint infections (9, 11).

Although most of the fluoroquinolones seem to be relatively safe (9, 13, 14), postmarketing surveillance studies have identified potentially severe adverse events. These include anaphylaxis, QTc-interval prolongation, and potential cardiotoxicity. Moreover, some fluoroquinolone agents have either been removed from the market (temafloxacin and grepafloxacin), or have been restricted in their use due to liver toxicity (trovafloxacin) (15). The most frequently observed adverse effects of fluoroquinolones are of gastro-intestinal origin, followed by mild neurological disorders (headache and dizziness) and skin reactions (14, 16). Rheumatological adverse effects are rare and consist mainly of myalgia, arthralgia and arthritis (17). Since animal studies have shown that fluoroquinolones may damage juvenile weightbearing joints, most fluoroquinolones are contra-indicated in children, and during pregnancy and lactation (14, 17, 18).

Shortly after their introduction, case reports associated the use of norfloxacin and ciprofloxacin with tendinitis (19, 20), and the first case of Achilles tendon rupture in a fluoroquinolone-treated patient was published in 1991 (21). During the past years, the number of reports of fluoroquinolone-associated tendinitis with or without rupture has risen (22-31), most likely because of the increased use of fluoroquinolones. Both tendinitis and especially tendon ruptures are serious injuries that may lead to substantial morbidity. Tendon ruptures often require surgical treatment. The potential mechanisms of fluoroquinolone associated tendon disorders will be discussed in chapter 8. This thesis focuses on the epidemiological assessment of this problem. Although many case reports on tendon disorders attributed to the use of fluoroquinolones have been published, there is little quantitative information on the risks of such disorders (32). Moreover, it is unknown whether particular patients are at high risk for developing such a disorder.

The studies presented in this thesis represent the different stages of pharmaco-epidemiology: from identifying a signal to quantification of the association, and the assessment of risk factors and effect modifiers. Chapter 2 describes the utilisation of fluoroquinolones in the Netherlands in the period 1991-1996. In this chapter, the utilisation of fluoroquinolones in the Netherlands is compared to the utilisation in several other western countries. In chapter 3, we describe 42 Dutch case-reports of fluoroquinolone-associated tendon disorders. The potential public health impact of the association between fluoroquinolone use and tendon rupture

is described in chapter 4. Chapter 5, 6, and 7 focus on the quantification and the determinants of the association between fluoroquinolone use and tendon disorders. In chapter 5, the outcome of interest consists of the association between fluoroquinolones and all forms of tendinitis. In chapter 6, the focus is on the association between fluoroquinolones and Achilles tendon disorders whereas chapter 7 presents the association of fluoroquinolones with Achilles tendon ruptures and the effect modification by determinants such as age and concurrent use of corticosteroids. Finally, chapter 8 summarises the main findings and includes a discussion on the methodology, and comments on clinical relevance as well as suggestions for further research.

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CHAPTER 2

UTILISATION OF FLUOROQUINOLONES IN THE NETHERLANDS

COMPARISON TO OTHER COUNTRIES

ABSTRACT

Introduction

In the Netherlands, fluoroquinolones are positioned as 'second line' antibiotics in order to prevent susceptibility to misuse and to reduce the risk of resistance. Recently, however, resistant strains to fluoroquinolones and serious adverse effects have been reported. In this study, we evaluate the patterns of fluoroquinolone use in the Dutch community and compare these patterns to those in other developed countries.

Methods

We used the PHARMO drug database to estimate the extent of fluoroquinolone use in the Dutch community. We identified all prescriptions for fluoroquinolones in the period 1991-1996. The number of defined daily doses (DDD) per 1000 inhabitants per day was used to determine the rate of exposure to fluoroquinolones. To estimate the use of fluoroquinolones in Australia, Canada, Finland, France, Germany, Italy, Norway, Spain, and the USA, we converted sales data on fluoroquinolones to DDD.

Results

In the Netherlands, the number of DDD per 1,000 inhabitants per day increased by 111% from 0.27 in 1991 to 0.57 in 1996. In this period, use of ofloxacin increased by 900%, use of ciprofloxacin by 133%, and use of norfloxacin by 76%. For all age classes, there was an increase in use but for persons above 60 years of age the increase was highest. In Canada, Germany, Italy, Spain, the UK, and the USA, there was an overall steady increase in use of fluoroquinolones. On the contrary, there was a temporary decrease in fluoroquinolone use in France and Australia after 1994. We observed a large heterogeneity in use of individual fluoroquinolones in the different countries.

Conclusion

Susceptibility to misuse of efficacious antibiotics is of great concern when improving rational use of drugs. Bacterial resistance, inefficacious use due to inappropriate diagnosis, and unnecessary adverse effects need to be prevented. We observed a strong increase in the use of fluoroquinolones in the Dutch community, in particular for ciprofloxacin and ofloxacin. When compared to other developed countries, however, the overall use of fluoroquinolones in the Netherlands was relatively low.

INTRODUCTION

Antibacterial agents are among the most frequently prescribed drugs in developed countries (1, 2). Unfortunately, improper use of these drugs is common. This may lead to rapid development of bacterial resistance, inefficacy, and unnecessary adverse reactions (3-6). Treatment guidelines have been developed to rationalise the use of antibacterial agents. Regular evaluation of antibiotic use may contribute to the rational use of these agents (7, 8).

Fluoroquinolones form a relatively new class of antibacterial agents which act by inhibiting bacterial DNA gyrase (topoisomerase II) (9). Because of their pharmacokinetic properties, excellent oral bioavailability, and relatively broad antibacterial activity, these drugs are increasingly used in western countries. As with other antibacterial agents, however, initial optimism about fluoroquinolones has been tempered by the development of resistant strains (10) and serious adverse effects such as psychoses, convulsions, anaphylaxis, QTc-interval prolongation, liver toxicity, and tendon ruptures (11, 12).

In the late eighties, the first fluoroquinolones norfloxacin, ofloxacin, ciprofloxacin and pefloxacin were introduced in the Netherlands. To decrease the risk of development of resistance, these drugs were positioned as 'second line' antibiotics (13). Recently, however, fluoroquinolone-resistant strains of *Pseudomonas aeruginosa*, *Neisseria gonorrhoea*, and *Staphylococcus aureus*, have been reported (14, 15). Furthermore, several cases of tendon rupture and psychiatric reactions associated with fluoroquinolones have been reported (16).

The objective of this study was to evaluate the pattern of fluoroquinolone use in the Dutch community in the period 1991 to 1996, and to compare this pattern with the pattern in other developed countries.

METHODS

Data source

In this study, we used the PHARMO drug database to estimate the extent of fluoroquinolone use in the Dutch community. This system includes the drug-dispensing records from community pharmacies of all 300,000 inhabitants of six medium-sized cities in the Netherlands. Because almost all patients designate a single pharmacy to fill their prescriptions from general practitioners or medical specialists, the dispensing histories are virtually complete for non-hospitalised use. The computerised drug dispensing histories include data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the

prescribed dose regimens, and the legend duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The PHARMO database, established in 1989, includes data back to 1986 for some cities. Since 1990, it has been continuously updated. PHARMO data relate only to outpatient antibiotic use. To estimate the use of fluoroquinolones in other developed countries, we used data on sales of fluoroquinolones which were provided by IMS HEALTH, the Netherlands. These data relate only to sales of fluoroquinolones via community pharmacies.

Drug utilisation

In the PHARMO database we identified all patients who filled at least one prescription for a fluoroquinolone (ATC-code: J01MA) in the period 1991-1996. For each filled drug prescription, the length of a treatment episode was calculated by dividing the total number of dispensed units by the prescribed daily dosage (PDD). We used the number of defined daily doses (DDD) per 1,000 inhabitants per day to determine the rate of exposure to fluoroquinolones. The DDD is a technical measurement unit giving the assumed average daily maintenance dose for an adult for the main indication. The DDD/1,000 inhabitants per day is a convenient tool to compare antibiotic drug use between different settings, regions, or even countries (17). In addition, we estimated the annual exposure prevalence expressed as the number of users/1,000 inhabitants per year, and the volume of use (the number of prescriptions/1,000 inhabitants per year). Since the PHARMO population is by and large representative of the Dutch population, all figures were extrapolated to the Dutch population after standardisation for age and sex (18).

Data on sales of fluoroquinolones were obtained from Australia, Canada, Finland, France, Germany, Italy, Norway, Spain, and the USA, in the period 1991 - 1996. Data were retrieved as the number of packages of each proprietary brand sold every year in each country, and then converted to DDD/1,000 inhabitants/day.

RESULTS

The Netherlands

Table 1 presents the utilisation of fluoroquinolones in the Netherlands during the period 1991 to 1996. In 1996, approximately 2 percent (251,000 persons) of the Dutch population received at least one prescription for a fluoroquinolone.

Table 1

Ever use of fluoroquinolones, prescriptions, and defined daily doses (DDD) per 1000 inhabitants per day in the Netherlands during the period 1991 - 1996

Year	1991	1992	1993	1994	1995	1996
Total						
ever use#	7.02	8.42	10.19	13.06	15.13	16.13
prescriptions$	9.91	12.36	15.01	19.17	22.87	24.18
DDD•	0.28	0.32	0.39	0.49	0.57	0.57
Male						
ever use#	5.20	7.12	8.97	11.29	13.00	14.03
prescriptions$	7.47	10.54	13.57	17.29	20.47	21.14
DDD•	0.23	0.28	0.38	0.47	0.56	0.54
Females						
Ever use#	8.80	9.70	11.37	14.79	17.21	18.18
Prescriptions$	12.30	14.14	16.41	21.00	25.22	27.16
DDD•	0.32	0.36	0.40	0.50	0.59	0.61
0-29 years of age						
Ever use#	1.87	1.71	2.18	3.00.	3.41	3.56
Prescriptions$	2.27	2.23	2.92	3.87	4.32	4.36
DDD•	0.07	0.07	0.08	0.10	0.11	0.09
30-59 years of age						
Ever use#	6.16	6.78	7.98	11.05	13.15	13.29
Prescriptions$	8.28	9.53	11.46	15.41	18.75	18.52
DDD•	0.22	0.25	0.32	0.40	0.47	0.45
60+ years of age						
Ever use#	20.38	27.11	33.09	40.01	45.61	50.57
Prescriptions$	30.62	41.41	50.07	61.81	73.55	81.36
DDD•	0.86	1.03	1.24	1.53	1.83	1.93

\# number of users per 1000 inhabitants per year

$ number of fluoroquinolone prescriptions per 1000 inhabitants per year

• number of DDD per 1000 inhabitants per day

The estimated number (extrapolated from the PHARMO system) of filled fluoroquinolone prescriptions was approximately 380,000. During the period 1991 through 1996, the number of fluoroquinolone users increased by approximately 20% every year. The number of DDD per 1,000 inhabitants per day increased by 131% from 0.27 in 1991 to 0.57 in 1996. Norfloxacin accounted for 40% of this increase, ciprofloxacin for 31%, and ofloxacin for 29%.

Although the annual exposure prevalence and volume of use were higher for women than for men, we observed an increase in use for both females and males. The proportional increase in use in the period 1991-1996 was more or less the same in all age classes but was in absolute terms most pronounced among

persons above 60 years of age. More than sixty percent of the fluoroquinolones were utilised by patients of 60 years and older in 1996. Not only the extent of use but also the type of fluoroquinolone differed between males and females. Norfloxacin was most frequently used by women, and ofloxacin and ciprofloxacin (in patients over 40 years of age) were more frequently used by men.

Figure 1 shows the utilisation of individual fluoroquinolones over time. During the period 1991 through 1996 the use of ofloxacin increased by more than 600% from 0.02 to 0.15 DDD/1000 inhabitants per day. The use of ciprofloxacin remained stable until 1993, but increased in the period 1993 through 1996 by 133 % from 0.06 in 1993 to 0.14 DDD/1000 inhabitants per day in 1996. Norfloxacin use increased by 76 % from 0.16 in 1991 to 0.28 DDD/1000 inhabitants per day in 1996.

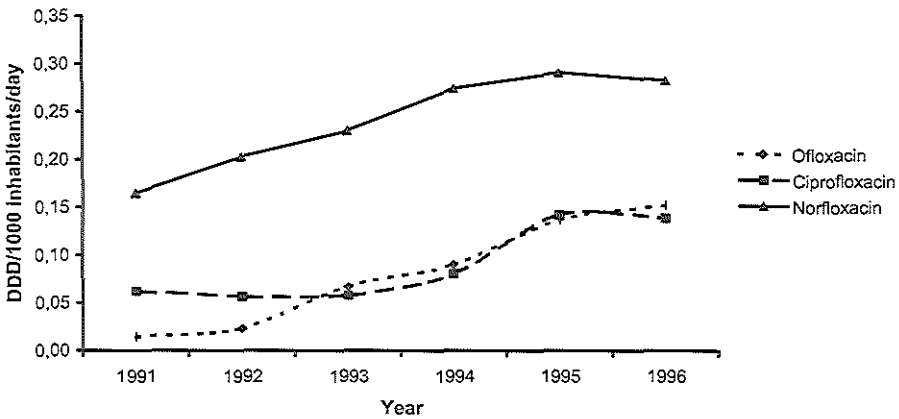

Figure 1
Utilisation of the different fluoroquinolones in the period 1991-1996

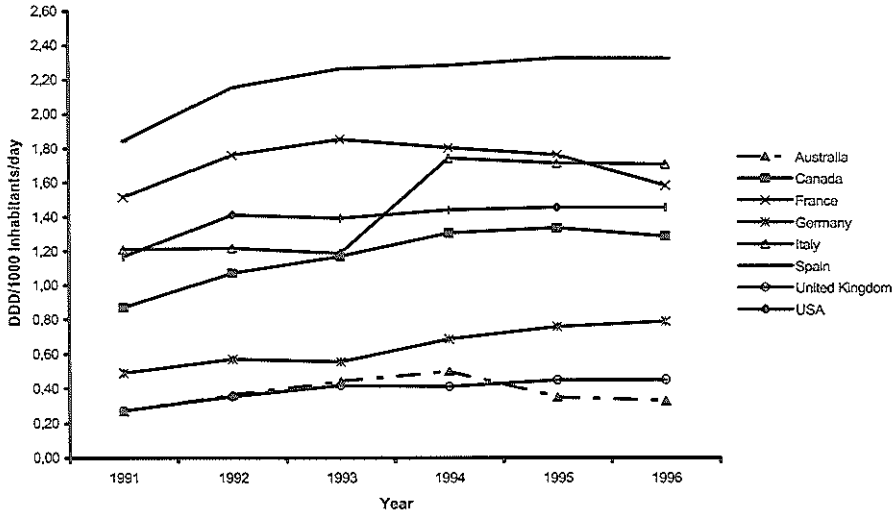

Figure 2

Sales of fluoroquinolones (DDD/1000 inhabitants/day) in Australia, Canada, France, Germany, Italy, Spain, United Kingdom, and United States in the period 1991-1996

Table 2

Sales of fluoroquinolones (DDD/1000 inhabitants per day) in Australia, Canada, France, Germany, Italy, Spain, United Kingdom, and the USA for the years 1991 and 1997, and percentage of change

Country	1991	1996	% Change
Australia	0.27	0.33	23.1
Canada	0.87	1.29	48.4
France	1.51	1.58	4.7
Germany	0.49	0.79	61.1
Italy	1.21	1.71	41.1
Spain	1.84	2.33	26.2
United Kingdom	0.27	0.45	65.7
USA	1.17	1.46	24.5

Other Countries

Figure 2 shows the utilisation of fluoroquinolones in Australia, Canada, France, Germany, Italy, Spain, the United Kingdom, and the USA. Except for France and Australia, there was an overall steady increase in the use of fluoroquinolones. In France, the use of fluoroquinolones increased from 1.51 DDD/1,000 inhabitants per day in 1991 to 1.85 in 1993, but declined to 1.58 in 1996. In Australia, the use of fluoroquinolones increased from 0.27 in 1991 to 0.50 DDD/1,000

inhabitants per day in 1994, but declined to 0.33 DDD/1,000 inhabitants per day in 1996. The strongest increase in use of fluoroquinolones in the other countries was in the United Kingdom, followed by Germany; and the lowest increase in the use of fluoroquinolones was in France (Table 2). In 1996, the use of fluoroquinolones was highest in Spain (2.33 DDD/1,000 inhabitants per day), and Italy (1.71 DDD/1,000 inhabitants per day); and lowest in Australia (0.33 DDD/1000 inhabitants per day), and the United Kingdom (0.45 DDD/1000 inhabitants per day). In Canada, France, Germany and the USA, the use of fluoroquinolones was respectively 1.29, 1.58, 0.79, and 1.46 DDD/1000 inhabitants per day in 1996.

Figure 3 presents the utilisation of the individual fluoroquinolones in Australia, Canada, France, Germany, Italy, Spain, the UK, and USA. Besides the differences in extent of use, there are also large international differences in the type of utilised fluoroquinolones. In Australia, the use of both ciprofloxacin and norfloxacin increased in the period from 1991 to 1994, and decreased thereafter. In Canada, the use of ciprofloxacin and ofloxacin increased, while the use of norfloxacin slightly decreased. In France, the use of ciprofloxacin increased but the use of norfloxacin, ofloxacin and pefloxacin decreased albeit not very substantial. In Germany, the use of both ciprofloxacin and ofloxacin increased by 118 and 64 percent respectively but the use of norfloxacin remained more or less stable. In Italy, the use of ciprofloxacin, lomefloxacin, and norfloxacin increased by 128, 116, and 25 percent respectively, while the use of ofloxacin decreased by 54 percent. In Spain, the use of ofloxacin and ciprofloxacin increased by 195 and 56 percent, while the use of enoxacin decreased by 74 percent. The use of norfloxacin remained stable during the study period. In the United Kingdom, the use of ciprofloxacin increased by 89 percent, while the use of norfloxacin and ofloxacin remained more or less stable. In the USA, the use of ciprofloxacin and ofloxacin increased by 33 and 71 percent respectively, while the use of norfloxacin and lomefloxacin decreased by 67 and 85 percent respectively.

DISCUSSION

In 1996, almost 2% of the Dutch population filled at least one prescription for a fluoroquinolone. The total number of DDD per 1,000 inhabitants per day of all fluoroquinolones was estimated at 0.57, which is comparable to the UK and Germany but much lower than that of Canada, France, Italy, Spain, and the USA. In Australia, however, the use of fluoroquinolones has been lower than in the Netherlands, most likely because of the Pharmaceutical Benefits Scheme (PBS)

prescribing restrictions (19). Norfloxacin was the most frequently used fluoroquinolone in the Netherlands, a situation that is similar to that in Australia, France, and Italy. In most other countries, ciprofloxacin has been the most frequently used fluoroquinolone. This might be explained by the predominant use of fluoroquinolones for urinary tract infections in the Netherlands, Australia, France, and Italy and for respiratory tract and gastro-intestinal infections in the other countries (2, 20-22)

In the Netherlands, we observed from the PHARMO database that the use of ciprofloxacin, norfloxacin and ofloxacin increased with age and that the use varied by sex. For norfloxacin, the high utilisation by females may be explained by its frequent use for the treatment of urinary tract infections. The high use of ofloxacin and ciprofloxacin by the elderly male may be explained by frequent treatment of prostatitis and respiratory infections (23, 24). Additionally, the higher use of fluoroquinolones by the elderly, in general, might be explained by the higher frequency of recurrent and complicated infections (24). Unfortunately, we did not have data on the indications and, therefore, we cannot exclude other explanations.

Like in many countries, a large increase in use of fluoroquinolones was observed in the Netherlands during the period 1991 through 1996. The total number of DDD per 1,000 inhabitants per day increased from 0.28 in 1991 to 0.57 in 1996. This rise in fluoroquinolone use is in line with the increased use in Canada, Germany, Italy, Spain, the UK, and the USA (21). In Australia and France, however, there was a temporary decrease in fluoroquinolone use which can be ascribed to recent changes in reimbursement (7, 19, 25). Since we are not aware of an increase in the rate of infections during the study period, and since the approved indications for fluoroquinolones did not essentially change, the observed rise in use suggests that fluoroquinolones are being prescribed more easily and are no longer mainly restricted to second-line treatment. For example, the steep increase in the population exposure prevalence of ciprofloxacin and ofloxacin in the Netherlands and other countries indicates more frequent use for the treatment of respiratory tract infections (22, 26). Here, there is a clear risk of susceptibility to misuse as respiratory tract infections are often self-limiting and frequently caused by viruses or by less sensitive pathogens such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*. General use of fluoroquinolones for such mild indications increases the risk of development of resistance and unnecessary occurrence of adverse effects. This is of major concern since there is a strong association between the magnitude of use and the emergence and spread of antimicrobial-resistant strains (7, 27, 28). Unfortunately, we did not have data

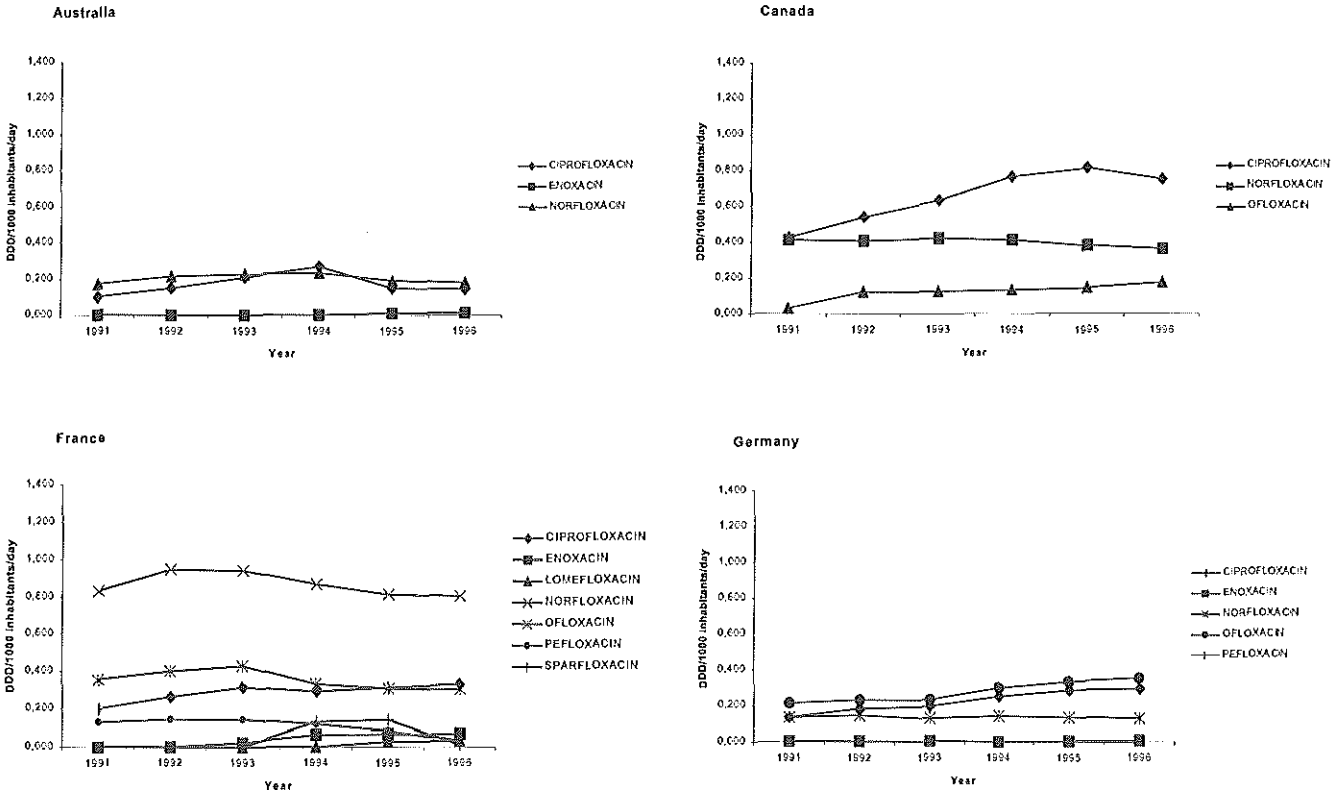

Figure 3a-d

Sales of individual fluoroquinolones in Australia, Canada, France, and Germany during the period 1991-1996

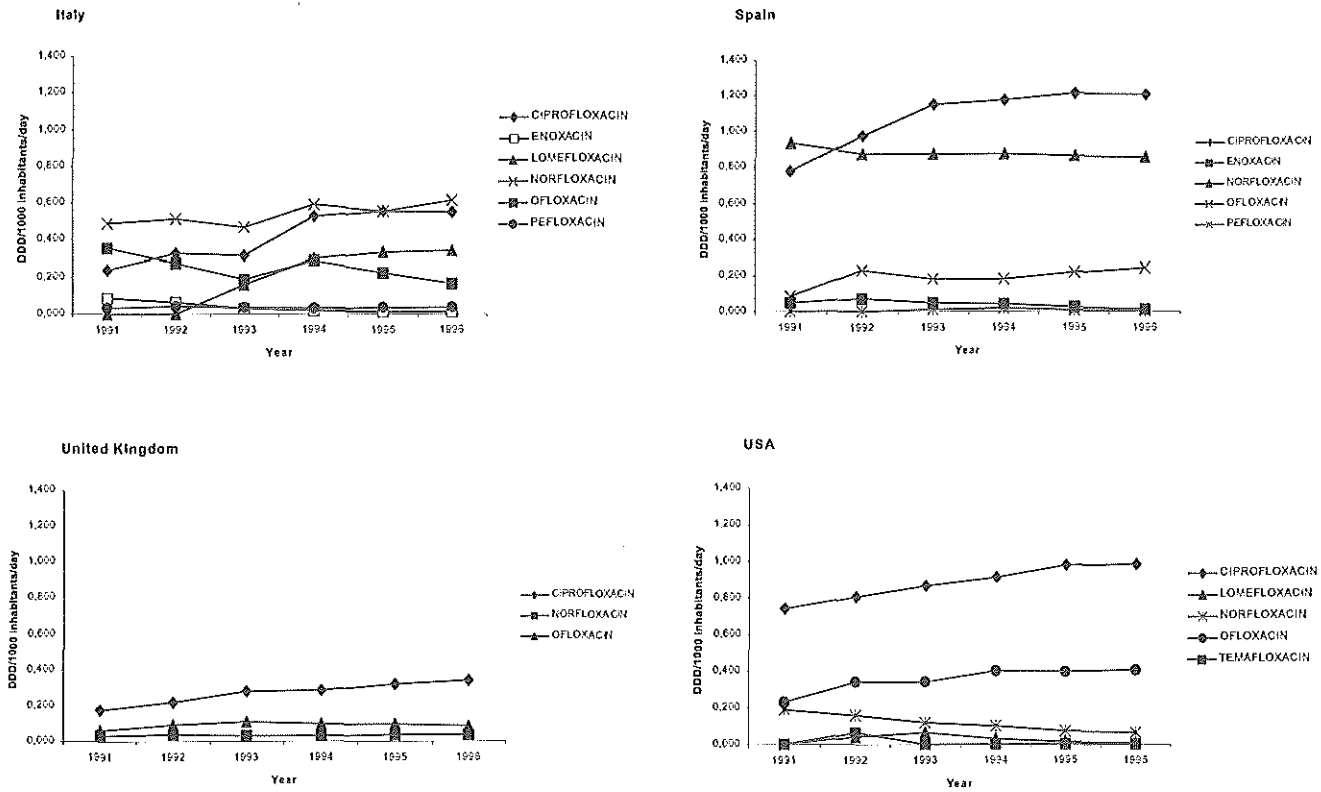

Figure 3e-h

Sales of individual fluoroquinolones in Italy, Spain, UK, and USA during the period 1991-1996

on the indications and therefore we can only speculate on the appropriateness of fluoroquinolones use and on causes for the increasing use of fluoroquinolones such as increasing resistance to other antibiotics, familiarity with the drugs, better efficacy, and a relatively mild adverse reaction profile. The recent marketing approval of fluoroquinolones with an even broader antibacterial spectrum requires caution. To prevent susceptibility to misuse, these potent new antibiotics should be prescribed only in specific situations as second line treatment and should be prescribed with caution in general practice.

This study has some potential limitations. First, fluoroquinolone utilisation in the Netherlands was assessed with data from the PHARMO drug database whereas we had to convert sales data from IMS Health to utilisation parameters (e.g. DDD) for our comparison with the level of prescribing in other countries. No other data were available, however, and a comparison between the PHARMO data and IMS data for the Netherlands showed that these gave highly comparable results (data not shown). Second, we were not able to assess the utilisation of fluoroquinolones during hospital admission. Third, our data are limited to the period 1991-1996 and may not adequately represent more recent utilisation patterns.

In conclusion, we observed a strong increase in the use of fluoroquinolones in the Dutch community, in particular for ciprofloxacin and ofloxacin. In comparison to other countries the use of fluoroquinolones in the Netherlands remains relatively low. To warrant proper use of fluoroquinolones, regular prescription review and use of guidelines for antimicrobial treatment are recommended both in hospital as well as in general practice.

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CHAPTER 3

TENDON DISORDERS ATTRIBUTED TO FLUOROQUINOLONES

A STUDY ON 42 SPONTANEOUS REPORTS IN THE PERIOD 1988 TO 1998

ABSTRACT

Introduction

Fluoroquinolone antibiotics have been associated with tendinitis and tendon rupture. In this paper we report on the follow-up of 42 spontaneous reports of fluoroquinolone-associated tendon disorders.

Methods

This study is based on reports of fluoroquinolone-associated tendon disorders reported to the Netherlands Pharmacovigilance Foundation Lareb and the Drug Safety Unit of the Inspectorate for Health Care between January 1st, 1988 and January 1st, 1998. By means of a mailed questionnaire, we collected information on the site of injury, onset of symptoms, treatment and course of the tendon disorder, as well as information on possible risk factors and concomitant medication.

Results

Out of 50 mailed questionnaires, 42 (84%) were returned. The data concerned 32 (76 %) patients with a tendinitis and 10 (24 %) patients with a tendon rupture. Sixteen (38 %) cases were attributed to ofloxacin, 13 (31 %) to ciprofloxacin, 8 (19 %) to norfloxacin and 5 (12 %) to pefloxacin. There was a male predominance and the median age of the patients was 68 years. Most of the reports concerned the Achilles tendon, and 24 (57 %) patients had bilateral tendinitis. The latency period between the start of treatment and the appearance of the first symptoms ranged from 1 to 510 days with a median of 6 days. Most patients recovered within 2 months after cessation of therapy but 26% had not yet recovered at the moment of follow-up.

Conclusion

These reports suggest that fluoroquinolone-associated tendon disorders are more common in patients over 60 years of age. Ofloxacin was implicated most frequently relative to the number of filled prescriptions in the Netherlands.

INTRODUCTION

Fluoroquinolones are antibacterial agents which are commonly used because of their favourable pharmacokinetic properties, bactericidal action at low minimal inhibitory concentration, and broad antimicrobial spectrum (1, 2). The most frequently observed adverse effects are of gastro-intestinal origin, followed by mild neurological disorders (headache and dizziness), and skin reactions (2, 3). Rheumatological adverse effects are rare and consist mainly of myalgia, arthralgia and arthritis (4). Since animal studies have shown that fluoroquinolones may damage juvenile weightbearing joints, most fluoroquinolones are contra-indicated in children, and during pregnancy and lactation (4, 5). Recently, fluoroquinolones have been associated with tendinitis and (subsequent) tendon rupture (6-15). Tendinitis and especially tendon rupture are serious injuries that may lead to substantial morbidity. Tendon ruptures often require surgical treatment. Risk factors most frequently associated with fluoroquinolone-induced tendon disorders include age over 60, corticosteroid therapy, and renal failure (8, 9, 11, 13, 16, 17). Other well-established risk factors for tendon disorders include sporting activity, a history of musculo-skeletal disorders, or diabetes mellitus (18-21). The pathogenesis of fluoroquinolone-induced tendon disorders has not been clarified yet.

In this paper we report on the follow-up of 50 spontaneous reports of tendon disorders that were attributed to the use of fluoroquinolones and sent to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation Lareb.

METHODS

The spontaneous adverse reaction-reporting scheme in the Netherlands has operated since the early sixties. From 1988 to 1998 the former Netherlands Centre for Monitoring of Adverse Reactions to Drugs (currently: Drug Safety Unit) of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation Lareb received a total of 52 spontaneous reports of possible fluoroquinolone-induced tendon disorders. In order to obtain additional information we sent a postal questionnaire to all health care professionals who had reported these cases. We requested additional information on the site of injury, the onset of symptoms, treatment and course of the tendon disorder as well as the presence of possible risk factors such as a history of musculoskeletal

conditions, diabetes mellitus, inflammatory bowel disease, renal failure, and sporting activities. In addition, we requested information about concomitantly used medication from pharmacy dispensing records.

To estimate the extent of fluoroquinolone use in the Dutch community, we used the PHARMO drug database (22). This system includes the drug-dispensing records of community pharmacies of all 300,000 inhabitants of a sample of six medium-sized cities in the Netherlands

RESULTS

Between January 1st, 1988 and January 1st, 1998, the Drug Safety Unit of the Inspectorate for Health Care received 22 reports, and the Netherlands Pharmacovigilance Foundation received 30 reports of fluoroquinolone-associated tendon disorders. Since 2 of the 52 reports were reported to both reporting centres, a total of 50 reports could be used for further analysis. The number of reports per year varied from 1.4 per 100,000 prescriptions in 1991 to 4.2 per 100,000 prescriptions in 1996.

Forty-two (84%) questionnaires that were sent to the health care professionals who reported these cases were returned. Thirty-two (76 %) of those 42 patients had tendinitis and 10 (24 %) a tendon rupture. Sixteen (38 %) cases were attributed to the use of ofloxacin, 13 (31 %) to ciprofloxacin, 8 (19 %) to norfloxacin, and 5 (12 %) to pefloxacin (Table 1). The clinical details are given in table 2. There was a male predominance (76% males vs. 24% females), and 71 percent of the cases was over 60 years of age (median: 68; range: 18-91). In 38 (90 %) patients, the reported disorder was located in the Achilles tendon. In 22 (57 %) patients, the Achilles tendon disorder was bilateral, in 10 left sided and in 4 patients right sided. The other tendons affected were those of the patella (*musculus quadriceps femoris*) (n=1), the epicondyles (n=2) and the rotator cuff of the shoulder (n=1). The following symptoms were most frequently present: pain (n=40), functional disability (n = 26), edema (n = 24), redness (n=9), and warmth (n=9). Most patients recovered within 2 months after cessation of fluoroquinolone therapy, but in a substantial part (n = 11; 26 %) pain and disability had not recovered at follow-up. In 5 out of 10 cases with tendon rupture, the rupture was preceded by tendinitis. Five patients (50%) with tendon rupture underwent surgical treatment, but no histological examination was performed. The median latency period between start of fluoroquinolone treatment and the appearance of first symptoms was 6 days (range 1 - 510 days); in 93 percent of the cases the latency period was less than one month. The average

Table 1
Distribution of cases

Fluoroquinolone	Tendinitis		Tendon rupture		Total	
	N	(%)	N	(%)	N	(%)
Ofloxacine	12	(37.5)	4	(40.0)	16	(38.1)
Ciprofloxacine	8	(25.0)	5	(50.0)	13	(31.0)
Pefloxacine	5	(15.6)			5	(11.9)
Norfloxacine	7	(21.9)	1	(10.0)	8	(19.0)

duration of treatment was 14 days (range 2-81). Most patients used the fluoroquinolones according to the recommended daily dose. However, ofloxacin was used by 37 percent of the patients in a dosage that was twice the recommended daily dose.

Regarding the presence of other risk factors, 11 (26 %) patients had a history of joint complaints and 3 (7 %) a history of trauma. Two (5 %) patients suffered from rheumatoid arthritis, 7 (14 %) from osteoarthritis, 1 (2 %) from gout, 2 (5 %) from diabetes mellitus, 1 (2 %) from psoriatic arthritis, and 1 (2 %) from hyperparathyroidism. Two (5 %) patients were known to have chronic renal failure, but none of these patients had been treated with dialysis or had undergone renal transplantation, which are both known risk factors for tendon disorders. In half of those cases that were active sporters (n=6), the tendon disorder occurred during sport activities. Of 4 patients (10 %) the blood group was known, 3 had blood group O, and 1 patient had blood group B. Thirty-two (76 %) patients had used other drugs concomitantly with fluoroquinolones, the most frequently being anti-asthmatics (n = 14; 33 %), antithrombotics (n = 10; 24 %), H2-receptor antagonists and proton pump inhibitors (n = 8; 19 %), oral corticosteroids (n = 10; 19 %), and diuretics (n = 7; 17 %).

DISCUSSION

In this case series, we evaluated 42 Dutch reports of fluoroquinolone-associated tendon disorders. Overall, our case series suggests that fluoroquinolone-associated tendon disorders are more common in patients over 60 years of age. Related to the total number of prescriptions, ofloxacin was the fluoroquinolone that was implicated most frequently.

A causal relationship between the intake of fluoroquinolones and the appearance of tendon disorders is likely in the vast majority of the 42 cases. Risk factors were absent in most patients, and there was a clear temporal relationship between first intake of fluoroquinolones and the occurrence of tendon disorders.

Table 2

Characteristics of reports of Achilles tendon disorders

Sex	Age	Drug	Dose	Indication	TR	ADR	Localization	Outcome	Remarks/Risk factors
M	91	Ofloxacin	400 mg	Prostatitis	3	Achilles tendon rupture	Bilateral	Functional disability	RA,OA, RF
M	86	Ofloxacin	400 mg	COPD	17	Achilles tendon rupture	?	Recovered	DM, thoracic kyphosis
M	81	Ofloxacin	1200 mg	?	6	Achilles tendon rupture	Bilateral	Recovered 3 months	OA, RF
M	77	Ofloxacin	400 mg	UTI	23	Achilles tendon rupture	Left	Functional disability	
F	73	Ciprofloxacin	1000 mg	Pyelonefritis	2	Achilles tendon rupture	Bilateral	Functional disability	Hyperparathyroidism
F	78	Ciprofloxacin	1000 mg	URTI	13	Achilles tendon rupture	Left	Death	
F	77	Ciprofloxacin	1000 mg	Pneumonia	16	Achilles tendon rupture	Left	Recovered 2 months	OA
M	81	Ciprofloxacin	1000 mg	Prostatitis	3	Achilles tendon rupture	Left	Recovered	OA
M	72	Ciprofloxacin	1500 mg	Bronchitis	5	Achilles tendon rupture	Right	Recovered	
M	40	Norfloxacin	800 mg	UTI	6	Achilles tendon rupture	Right	Recovered	During sport
M	62	Ofloxacin	800 mg	RTI	5	Achilles tendinitis	?	Death	Bedridden
M	18	Ofloxacin	400 mg	Prostatitis	7	Achilles tendinitis	Bilateral	Recovered	Sport
M	41	Ofloxacin	400 mg	UTI	2	Achilles tendinitis	Bilateral	Persistent symptoms	Sport
M	75	Ofloxacin	400 mg	Epididymitis	7	Achilles tendinitis	Bilateral	Recovered	PAD
F	70	Ofloxacin	400 mg	RTI	3	Achilles tendinitis	Bilateral	Recovered	
M	47	Ofloxacin	200 mg	Bronchitis	21	Achilles tendinitis	Bilateral	Recovered	Psoriasis
M	79	Ofloxacin	800 mg	Bronchitis	1	Achilles tendinitis	Bilateral	Recovered 1 week	
F	49	Ofloxacin	400 mg	RTI	20	Achilles tendinitis	Bilateral	Recovered	Thoracic kyphosis
M	72	Ofloxacin	800 mg	COPD	10	Achilles tendinitis	Bilateral	Recovered	
M	64	Ofloxacin	800 mg	Bronchitis	1	Achilles tendinitis	Right	Recovered	
M	46	Ciprofloxacin	500 mg	UTI	1	Achilles tendinitis	Bilateral	Recovered 10 days	
M	66	Ciprofloxacin	1000 mg	Prostatitis	150	Achilles tendinitis	Bilateral	Recovered 2 weeks	Gout
M	68	Ciprofloxacin	500 mg	COPD	5	Achilles tendinitis	Bilateral	Recovered	

Sex	Age	Drug	Dose	Indication	TR	ADR	Localization	Outcome	Remarks/Risk factors
F	62	Ciprofloxacin	1000 mg	Sinusitis	2	Achilles tendinitis	Bilateral	Recovered	
M	75	Ciprofloxacin	1000 mg	RTI	4	Achilles tendinitis	Bilateral	Recovered	
M	45	Ciprofloxacin	750 mg	Enteritis	8	Achilles tendinitis	Left	Atrophic leg	Sport
M	75	Ciprofloxacin	1000 mg	RTI, COPD	5	Achilles tendinitis	Bilateral	Recovered 8 months	
M	64	Pefloxacin	800 mg	Prostatitis	4	Achilles tendinitis	Bilateral	Recovered 3 months	
M	74	Pefloxacin	800 mg	Catheter inf.	1	Achilles tendinitis	Bilateral.	Recovered	
M	47	Pefloxacin	800 mg	Prostatitis	?	Achilles tendinitis	Bilateral.	Recovered	RA, sport
M	67	Pefloxacin	800 mg	Prostatitis	25	Achilles tendinitis	Bilateral.	Recovered	Obese
F	84	Norfloxacin	800 mg	UTI	4	Achilles tendinitis	Bilateral.	Recovered	
M	76	Norfloxacin	800 mg	Prostatitis	13	Achilles tendinitis	Left	Recovered	DM
F	58	Norfloxacin	800 mg	UTI	5	Achilles tendinitis	Left	Recovered	
F	52	Norfloxacin	400 mg	Trigonitis	81	Achilles tendinitis	Left	Recovered	Fibromyalgia
M	70	Norfloxacin	400 mg	Prostatitis	8	Achilles tendinitis	Left	Recovered	History of tuberculous spondylitis
F	64	Norfloxacin	800 mg	UTI	7	Achilles tendinitis	left	Recovered	
M	68	Pefloxacin	800 mg	Prostatitis	?	Achilles tendinitis	right	Recovered 1.5 year	OA
M	64	Ofloxacin	400 mg	UTI	3	Epicondylitis medialis	Bilateral	Recovered	During sport
M	56	Ofloxacin	400 mg	Prostatitis	1	Tendinitis patella	Right	Recovered	
M	77	Ciprofloxacin	1000 mg	RTI	510	Tendinitis rotator cuff shoulder	Left	Recovered	
M	53	Norfloxacin	800 mg	UTI	5	Epicondylitis lateralis	Left	Recovered 2 months	DM

TR = time relationship in days between first intake and tendon disorder; DB = diabetes mellitus; OA = osteoarthrose; RA = rheumatoid arthritis; PAD = peripheral arterial disease; RF = renal failure; UTI = urinary tract infection; RTI = respiratory tract infection

Moreover, several similar cases have been reported in the medical literature (6-16, 23-25).

It remains unclear through which mechanism fluoroquinolones may cause tendon disorders in humans. Because of fluoroquinolone-induced arthropathy that has been described in various juvenile animal species after high-dose administration of fluoroquinolones (4, 5), most fluoroquinolones are contraindicated in children. Japanese researchers succeeded to produce fluoroquinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin, but not in adult rats (26). An in vitro-study showed that the viability of rabbit tenocytes was altered by fluoroquinolones, and that this effect occurred at concentrations that are comparable to therapeutic concentrations (27). The sudden onset of some tendinopathies, occasionally after a single dose of a fluoroquinolone, suggests a direct toxic effect on collagen fibres. Only a few histopathological studies in humans have been performed. In two studies neovascularisation, interstitial edema, and severe degenerative lesions were found, but no inflammatory cell infiltrate, which is compatible with an ischemic process (8, 28). Another study showed abnormal fibre structure and arrangement, hypercellularity, and increased interfibrillar glycosaminoglycans (14). The fact that the former histopathological findings are similar to those in overuse conditions in athletes gives credence to the potential that fluoroquinolones alter cellular function, creating an excess production of the non-collagenous extracellular matrix and a subsequent change in cell to matrix ratio (14).

Fluoroquinolones were associated with tendinitis for the first time in 1983 (23), the first case of Achilles tendon rupture in a fluoroquinolone-treated patient did not appear until 1991 (29, 30). Subsequently, the number of reports of fluoroquinolone associated tendinitis with or without rupture increased (6-16, 23-25), together with an expansion in use of fluoroquinolones (31, 32). Most of the reports originate from France, which may be caused by the large publicity in that country. In the vast majority of the previously reported cases, the Achilles tendon was affected with painful tendinitis or rupture (6-8, 10-13, 16, 23, 28, 33, 34), but other tendons like the tendons of the *musculus biceps brachii* (35), the *musculus supraspinatus* (12), the *musculus extensor pollicis longus* (36), and the epicondyles (24) may also be affected. As in our case series, pain was the leading symptom, but edema, functional disability and itching were also present in those case series. A finding in both literature and our case-series is that in over 50 percent of the cases there was bilateral involvement of tendons (8, 12, 13). The latency period between start of treatment and onset of symptoms was usually two weeks, sometimes even a few days (8, 9, 12, 13, 16), which is consistent with our

data. Duration of recovery was variable, and a substantial part had persistent symptoms in the previously reported cases. In our study 26 % of the patients had persistent complaints of pain and disability which had not yet recovered at the moment of follow-up. Of the different fluoroquinolones, pefloxacin has been implicated most frequently, followed by ofloxacin. In our study, we had relatively little cases to pefloxacin probably because of its modest market share. Tendinitis by other fluoroquinolones such as ciprofloxacin, norfloxacin, enoxacin and lomefloxacin has been reported, but the incidence seems to be much lower. In our case series most of the reports concerned ofloxacin.

Risk factors most frequently associated with fluoroquinolone-induced tendon disorders include age over 60, corticosteroid therapy, and end stage renal failure (12-14, 16, 37). In our study 71 percent of the patients was over 60 years of age, and 20 percent used corticosteroids concomitantly. Only 2 patients had renal failure, and none of the cases had been dialysed.

Despite the relatively large volume of case-based evidence, surprisingly little is known about the epidemiology of fluoroquinolone-induced tendinitis and tendon rupture. Epidemiological evidence is limited to one cohort study that showed that the risk of Achilles tendinitis to fluoroquinolones, especially ofloxacin, is higher than the risk to other antibacterial drugs (38). In this study the incidence rate of tendinitis to fluoroquinolones was 2.9 per 1,000 prescriptions. On the other hand, no cases of Achilles tendon rupture were found in 2,122 ciprofloxacin-treated patients (39). With prescription-event monitoring a frequency rate of 2.4 per 10,000 patients was found for tendinitis, and 1.2 for tendon rupture, respectively (40). In our study the estimated frequency of tendon disorders among fluoroquinolone users was 4 per 100,000 prescriptions, which suggests that underreporting is substantial. In a study, done with data from the French spontaneous reporting system, the estimated frequency of tendon disorders among fluoroquinolone users was 20 per 100,000 prescriptions (12).

In conclusion, in this study we reported on 42 cases of tendinitis or tendon rupture after fluoroquinolone therapy. Despite numerous case reports on fluoroquinolone-induced tendinitis or tendon rupture, quantitative information on this subject is scanty. Physicians who prescribe a fluoroquinolone should seriously consider stopping or changing therapy at the first sign of this reaction, given the potential severe disability.

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CHAPTER 4

FLUOROQUINOLONE USE AND THE CHANGE IN INCIDENCE OF TENDON RUPTURES IN THE NETHERLANDS

ABSTRACT

Introduction

Shortly after their introduction, fluoroquinolones were associated with reports of tendinitis and tendon rupture. During the past years, the number of reports has risen, possibly because of an increased use of fluoroquinolones. In this study, we describe the use of fluoroquinolones in the Dutch community and the possible public health effects of an association between fluoroquinolone use and tendon ruptures.

Methods

In the PHARMO drug database we identified all prescriptions for fluoroquinolones in the period 1991-1996. The incidence of fluoroquinolone use was expressed as the number of fluoroquinolone episodes per 1000 inhabitants in one year, and extrapolated to the Dutch population after standardisation on age and gender. The annual incidence of non-traumatic tendon ruptures in the period 1991-1996 was calculated with data from the nation-wide hospital registry. The expected number of fluoroquinolone-attributable tendon ruptures was calculated on the basis of the use of fluoroquinolones, the number of non-traumatic tendon ruptures, and an assumed relative risk of 1.5-10.

Results

In 1996, approximately 251,000 patients experienced 318,000 episodes of fluoroquinolone use in the Netherlands. Females used fluoroquinolones more often than males, and the number of episodes increased exponentially with age. In the period 1991 through 1996, the absolute number of fluoroquinolone episodes increased by 160%, from 122,000 to 318,000. The absolute number of hospitalised tendon ruptures increased with 28%, from 768 in 1991 to 984 in 1996. Assuming a relative risk of 1.5 to 10.0, 1 to 15 tendon ruptures could be attributed to fluoroquinolone use in 1996. Only 7 % of the observed increase could be attributed to the increased use of fluoroquinolones. If the total increase of hospitalised non-traumatic tendon ruptures would be attributable to the increase in fluoroquinolone use, this would mean that the risk of non-traumatic tendon ruptures to fluoroquinolones would be more than 250 times the risk during non-use.

Conclusion

In the Netherlands, a large simultaneous increase in non-traumatic tendon ruptures and fluoroquinolone use was observed in the period between 1991 to 1996. Assuming a relative risk of 1.5 to 10.0 for tendon ruptures during fluoroquinolone use, only 0.5 to 7% of the increase in non-traumatic tendon ruptures could be attributed to the increased fluoroquinolone use. The increase in the incidence of non-traumatic hospitalised tendon ruptures in the Netherlands is not likely to be explained solely by the increased use of fluoroquinolones.

INTRODUCTION

Fluoroquinolones form a relatively new class of antibacterial agents that act by inhibiting bacterial DNA gyrase (topoisomerase II) (1). In general, fluoroquinolones are well tolerated, have good pharmacokinetic properties, bactericidal action with low minimal inhibitory concentration, and a broad antibacterial activity spectrum (2). The most frequently observed adverse effects are of gastro-intestinal origin, followed by CNS disorders and skin reactions (3-5).

In the mid eighties, the first representatives of this group, norfloxacin, ciprofloxacin, ofloxacin, and pefloxacin were registered in several countries. Shortly after their introduction, however, anecdotal case reports associated the use of norfloxacin and ciprofloxacin with tendinitis (6, 7) and in 1991, the first case of Achilles tendon rupture in a fluoroquinolone-treated patient was published (8). During the past years, the number of reports of fluoroquinolone-associated tendinitis with or without rupture has risen, possibly because of an increased use of fluoroquinolones (9-18). To date, 50 cases of fluoroquinolone-attributed tendon disorders have been reported to the Dutch Authorities, and nearly 1,000 cases have been reported worldwide to the WHO Collaborating Centre for International Drug Monitoring (19). In the vast majority of cases, the Achilles tendon was affected with painful tendinitis or rupture, very often occurring within one month after start of treatment (14, 16, 17).

Although many case reports on tendon disorders attributed to the use of fluoroquinolones have been published, there is little quantitative information on the risks of such disorders (20). In an earlier study, we found an almost 3-fold increase of risk of tendinitis to fluoroquinolones, especially involving the Achilles tendon. In this study, ofloxacin had the strongest association with Achilles tendinitis (RR = 7.6; 95%CI: 1.7-34.6 (21). To determine the possible public health effects of such an association, we estimated the expected number of cases in the Netherlands based on the extent of use of fluoroquinolones, the number of non-traumatic tendon ruptures, and an assumed relative risk of 1.5-10.0.

METHODS

Data sources

In this study, we used the PHARMO drug database to estimate the extent of fluoroquinolone use in the Dutch community. This system includes the drug-dispensing records of community pharmacies of all 300,000 inhabitants of six medium-sized cities in the Netherlands. Because almost all patients designate a single pharmacy to fill their prescriptions, the dispensing histories are virtually complete for outpatient drug use. The computerised drug dispensing histories contain data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed daily dose regimen, and the legend duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Data from the nation-wide hospital discharge registry of the Dutch Centre for Health Care Information (SIG) were used to calculate the annual incidence of hospitalised non-traumatic tendon ruptures (ICD-9CM code 727.6) presented in clinical and day-care. This centre maintains a unique register containing data on all patients discharged from hospitals in the Netherlands. The anonymous hospital admission records contain one principal discharge diagnosis (obligatory) and up to 9 additional (optional) diagnoses. The data are confidential and are not used for reimbursement procedures. All diagnoses are coded according to the International Classification of Diseases (ICD-9-CM).

Drug utilisation

In the PHARMO drug database we identified all patients that ever filled a prescription for a fluoroquinolone (ATC-code: J01MA) in the period 1991-1996. For each filled drug prescription, the length of a treatment episode was calculated by dividing the total number of dispensed units by the prescribed daily dosage (PDD).

We calculated the incidence of fluoroquinolone use (number of episodes per 1,000 inhabitants per year) to determine the extent of exposure to fluoroquinolones in the PHARMO population. As the PHARMO population is by and large representative of the Dutch population (22), all figures were extrapolated to the Dutch population after standardisation on age and gender. Subsequently, the standardised incidence estimates were used to calculate the 'population' exposure prevalence per month (episodes/10,000 persons).

Estimation of potential public health effects

The number of patients in the Netherlands who might run the risk of developing a tendon rupture to fluoroquinolone use was estimated in a two step analysis. In step 1, the proportion of tendon ruptures in the Netherlands that can be attributed to fluoroquinolone use was estimated by calculating the Population Attributable Risk (PAR) percentage using the following formula: .

$$PAR = \frac{p(RR-1)}{1+p(RR-1)}$$

In this formula p is defined as the 'population' exposure prevalence of fluoroquinolone use and RR as the relative risk of tendon rupture associated with exposure to fluoroquinolones (23). The RR for tendon rupture was varied between 1.5 to 10.0, based on a RR for tendinitis of 3.0 as no risk estimates were available for tendon ruptures (21). The PAR therefore, is an estimate of the proportion of tendon ruptures in the total population that can be attributed to use of fluoroquinolones, conditional that there is a causal relationship between fluoroquinolone exposure and tendon disorders.

In step 2, the population attributable risks for the different RRs were multiplied with the number of non-traumatic hospitalisations for a tendon rupture in one year in the Dutch population to get the expected number of fluoroquinolone-attributed tendon ruptures in the Netherlands. Data from the SIG hospital discharge registry were used to calculate the annual incidence of hospitalised non-traumatic tendon ruptures (ICD-9CM code 727.6) in the period 1991-1996. Only the principal discharge diagnosis was used.

RESULTS

Utilisation of fluoroquinolones

In 1996, approximately 251,000 patients experienced 318,000 episodes of fluoroquinolone use in the Netherlands. This means that approximately 2 percent of the Dutch population was at least once exposed to fluoroquinolones in 1996. The use of norfloxacin accounted for 52% of all fluoroquinolone episodes, ciprofloxacin for 27%, and ofloxacin for 21%. There were no users of pefloxacin. Overall, females used fluoroquinolones more often than males, although opposite rates were observed in several age groups. Fluoroquinolone use increased exponentially with age (Figure 1). More than 60% of the fluoroquinolones was used by patients of 60 years and older in 1996.

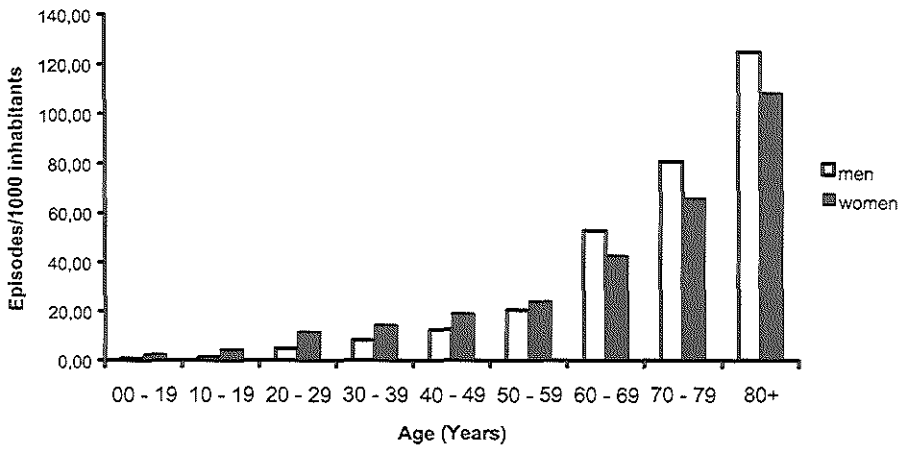

Figure 1
Incidence of fluoroquinolone use in 1996 by age and gender

In the period 1991 through 1996, the absolute number of fluoroquinolone episodes increased with 160%, from 122,000 to 318,000. Norfloxacin accounted for 41% of this increase, ciprofloxacin for 31% and ofloxacin for 29%. The incidence of fluoroquinolone use increased with 253 % from 8.1 episodes per 1,000 inhabitants in 1991 to 20.5 in 1996. This increase occurred in both genders, but mainly in persons above 60 years of age (Figure 2a and 2b).

Estimation of possible public health effects

Consistent with the increased incidence the 'population' exposure prevalence of fluoroquinolones use increased from 7 to 17 per 10,000 persons per month between 1991 and 1996. In the same period, the incidence of hospitalised non-traumatic tendon ruptures increased from 5.08 per 100,000 inhabitants to 6.32 per 100,000, whereas the absolute number of hospitalised non-traumatic tendon ruptures increased by 28% from 768 in 1991 to 984 in 1996 (Table 1). This increase occurred mainly in persons above 60 years of age (Figure 3a and 3b). There is a strong positive correlation between fluoroquinolone use and non-traumatic tendon ruptures over the different years. Based on the range of assumed relative risks of 1.5 to 10.0, it appears that 0.09 to 1.51 % of the admitted patients with non-traumatic tendon ruptures in the Netherlands was attributable to fluoroquinolone use in 1996. On the basis of these PARs, 1 to 15 tendon ruptures could be explained by fluoroquinolone use in the Netherlands in 1996 (Table 1), which is equivalent to 0.6 to 9.6 cases per 10 million inhabitants.

Table 1
Fraction of the community exposed to fluoroquinolones, number of tendon ruptures in the Netherlands, and Population Attributable Risk and expected ruptures during fluoroquinolone use with different relative risks, in the period 1991 – 1996

Year	Population exposure prevalence (episodes/10000 patients/month)	Number of ruptures in the Netherlands	RR = 1.5		RR = 10.0	
			PAR	Expected ruptures	PAR	Expected ruptures
1991	7	768	0,03	0,3	0,60	4,6
1992	8	786	0,04	0,3	0,74	5,8
1993	10	930	0,05	0,5	0,93	8,6
1994	13	922	0,07	0,6	1,18	10,9
1995	16	983	0,08	0,8	1,38	13,6
1996	17	984	0,09	0,8	1,51	14,9

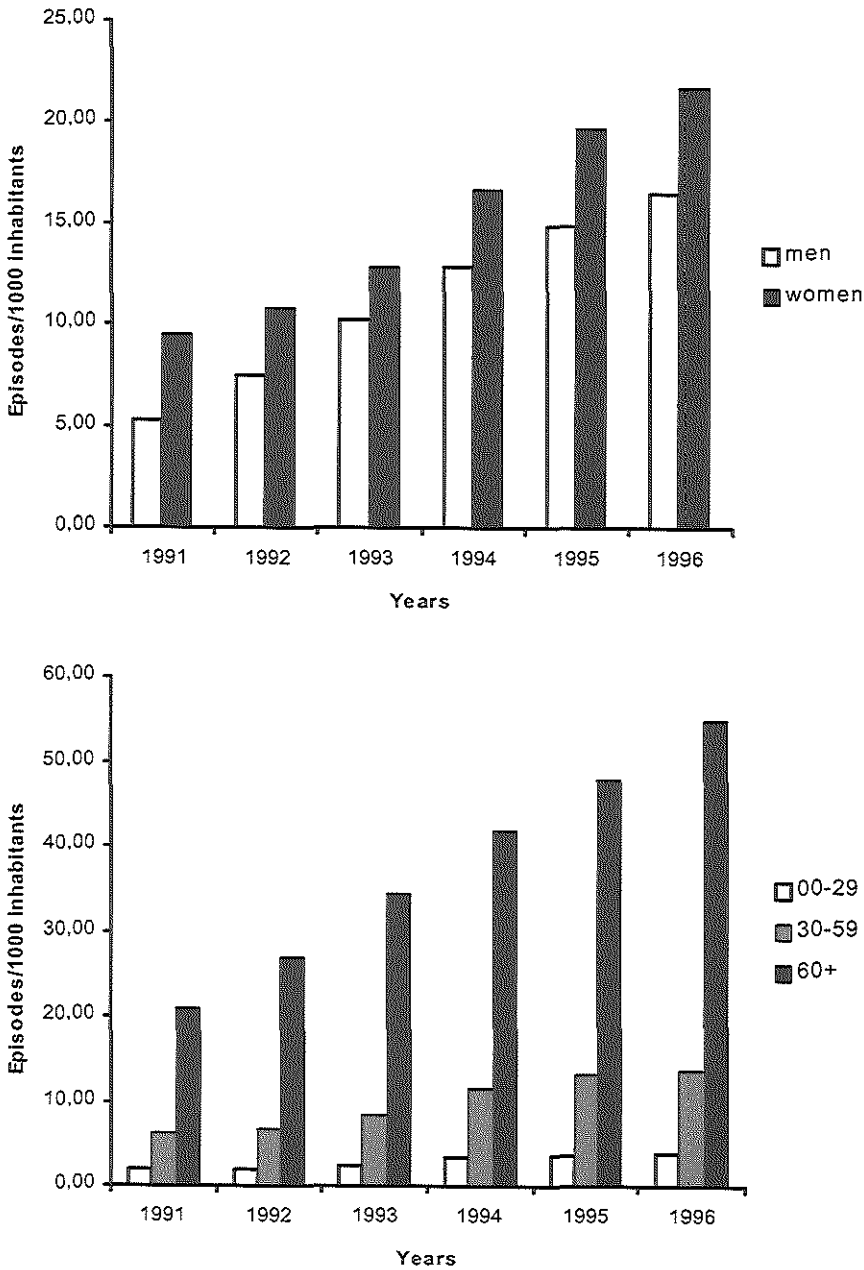

Figure 2a & b
Incidence of fluoroquinolone use in the period 1991-1996 stratified for gender and age

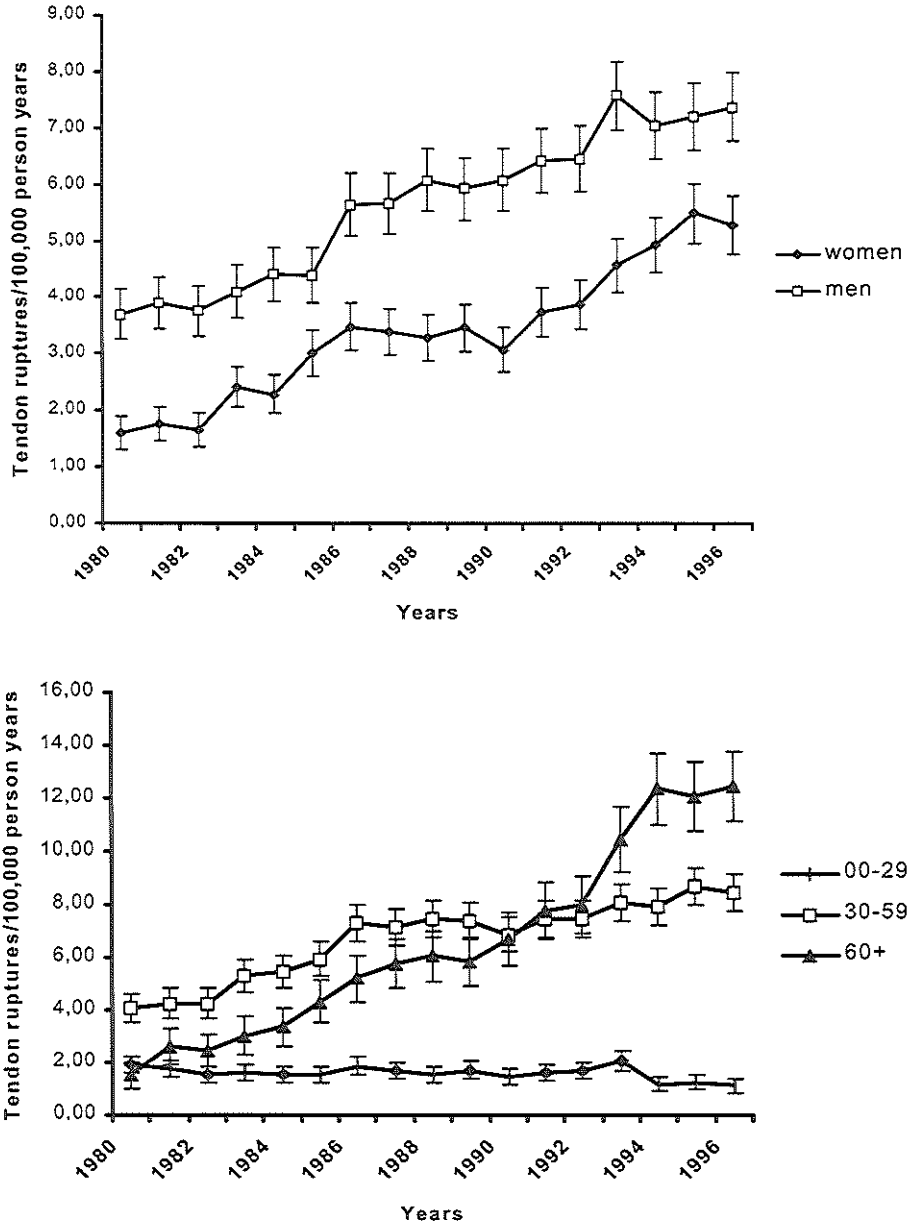

Figure 3a & b

Incidence of non-traumatic tendon ruptures in the period 1980-1996, stratified by gender and age

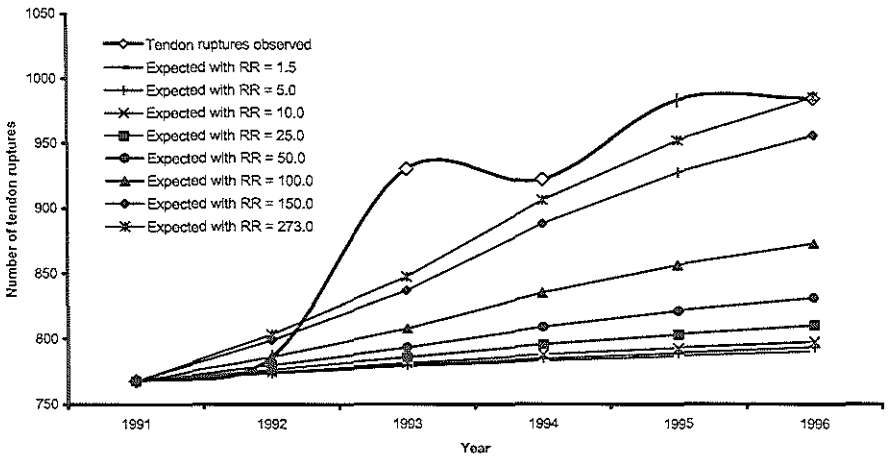

Figure 4

Absolute and expected number of hospitalised non-traumatic tendon ruptures per year in the Netherlands

Assuming a high relative risk of 10.0, only 7 % of the increase of non-traumatic tendon ruptures could be attributed to the increased use of fluoroquinolones. If the total increase of hospitalised non-traumatic tendon ruptures could be attributed to the increase in fluoroquinolone use, the risk of non-traumatic tendon ruptures to fluoroquinolones would be more than 250 times the risk during non-use (Figure 4).

DISCUSSION

We observed a large simultaneous increase in the number of case reports attributing tendon rupture to fluoroquinolones, the incidence of non-traumatic tendon ruptures, and the use of fluoroquinolones in the Netherlands in the last years. Despite this apparent correlation we estimated that public health impact is low since a maximum of only 15 cases per year can be attributed to the use of fluoroquinolones.

In the Netherlands, a large increase in the use of fluoroquinolones was observed in the period 1991 through 1996. The absolute number of fluoroquinolone episodes increased with 160%, from 122,000 in 1991 to 318,000 in 1996. This rise in fluoroquinolone use is in line with the increased use in England and Spain (24, 25), but in the Nordic countries (26) there was a decrease in fluoroquinolone use during this period. Fluoroquinolones were used more often by females, and utilisation increased exponentially with age. The high use

by women may be explained by relatively frequent treatment of urinary tract infections with norfloxacin. The increased use by the elderly might be due to more frequent and complicated infections.

Simultaneously with the strong increase in fluoroquinolone use, there was a substantial increase in non-traumatic tendon ruptures in the period 1991 to 1996. However, assuming a RR of 1.5-10.0 for tendon ruptures during fluoroquinolone use, only 0.5 – 7% (1 – 15 cases) of the increase in non-traumatic tendon ruptures could be attributed to the increased use of fluoroquinolones. Hence, it is not likely that the increase in the absolute number of non-traumatic hospitalised tendon ruptures in the Netherlands is solely explained by the increased use of fluoroquinolones. In that case the RR has to be more than 250. On the other hand, there is a strong positive correlation between fluoroquinolone use and non-traumatic tendon ruptures over the different years. Furthermore, the inclusion criteria for the diagnosis tendon rupture did not change in this period, and also increased sporting is not a likely explanation because the increase in hospitalised tendon ruptures occurred mainly in the age-class above 60 years.

Our study has several limitations. First of all, our utilisation figures are based on data from community pharmacies, and we had no detailed information on in-patient use of fluoroquinolones where the use can be substantial (27). Therefore, our figures are probably an adequate estimation of use in the community but an underestimation of the total use. This means that the population exposure prevalence and thus the PARs could be higher in the range of RRs that we used, and that slightly more cases could be attributed to the use of fluoroquinolones. However, even if the exposure prevalence would double, the maximum number of cases of tendon rupture that can be attributed to the use of fluoroquinolones would be 20 per 10 million inhabitants, which is still low. This number may increase in the future due the recently introduced fluoroquinolones levofloxacin, grepafloxacin and sparfloxacin, and the subsequently rising trend in fluoroquinolone use.

We may have underestimated the incidence and the total number of tendon ruptures since we restricted our search to non-traumatic tendon ruptures. Traumatic tendon ruptures were not included in our analyses as these are usually caused by accidents rather than by an adverse effect. Furthermore, we had no information on tendon ruptures that would not lead to hospital admission. It is, however, unlikely that we have a high underestimation of tendon ruptures in this study because in the Netherlands most of the tendon ruptures are admitted for surgery.

In conclusion, a large simultaneous increase in non-traumatic tendon ruptures and fluoroquinolone use was observed in the period 1991 - 1996, in the Netherlands. Based on a relative risk of 10, only 15 cases could be explained by the use of fluoroquinolones in 1996. Hence, we conclude that the increase in the absolute number of non-traumatic hospitalised tendon ruptures in The Netherlands is probably not solely caused by the increased use of fluoroquinolones.

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CHAPTER 5

A STUDY ON THE ASSOCIATION BETWEEN TENDINITIS AND FLUOROQUINOLONES

ABSTRACT

Introduction

In several case-reports, tendinitis has been attributed to the use of fluoroquinolones. The objective of this study is to determine whether there is an association between the 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 were obtained from the IPCI-database that contains 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, co-trimoxazole 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 identified through 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 1,841 users of fluoroquinolones and 9,406 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.

Conclusion

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

INTRODUCTION

In the past 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 two 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.

METHODS

Data source

Data were obtained from the Integrated Primary Care Information (IPCI) system, a research-oriented database with data from computerised patient records of general practitioners (GPs) throughout the Netherlands. The IPCI system 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 (1997), 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 registration status who were treated in the study period with one of the following antibacterial drugs: fluoroquinolones (index group), amoxicillin, trimethoprim, co-trimoxazole and nitrofurantoin (reference group). The latter four drugs were chosen as a reference because these are commonly-used antibiotics with a well-known safety profile and have not been associated with tendinitis. Subjects were required 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 one 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 one 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.

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

In step 2, a patient profile was generated and printed for all selected patients, 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 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 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 1000 days at risk. Incidence densities for exposure to fluoroquinolones were compared to 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 the 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 a 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 1,841 users of fluoroquinolones and 9,406 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).

Table 2
Characteristics of the patients in the index group and in the reference group

	Fluoroquinolones (index group)		Amoxicillin, trimethoprim, co-trimoxazole and nitrofurantoin (reference group)		
Number of users	1,841	(100.0%)	9,406	(100.0%)	
Gender					
Male	664	(36.1%)	2,693	(28.6%)	
Female	1,177	(63.9%)	6,713	(71.4%)	$p < 0.001$
Mean age	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		

In total, 418 patients received 500 prescriptions for ofloxacin, 456 patients received 556 prescriptions for ciprofloxacin, and 1,030 patients received 1,362 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 in 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 computerised 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

Table 3

The incidence densities stratified for achilles tendinitis and other tendinopathies among the drugs under study and relative risks stratified for achilles tendinitis and other tendinopathies

	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, co-trimoxazol, nitrofurantoin or trimethoprim

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 to fluoroquinolones was higher than the risk to a reference group of four commonly used antibacterial agents with a known safety profile. As these are no known causes of tendinitis, they represent the background risk and even if some of them incidentally cause tendinitis, this would tend to underestimate the RR to fluoroquinolones rather than overestimate it. Ofloxacin had the strongest association with Achilles tendinitis. Although age, gender, and number of visits to the GP differed significantly between the fluoroquinolone users and the users of other antibacterial drugs, adjustment for these factors did not take away 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 recognised 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 computerised search. We have tried to minimise 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 the fact that 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 to 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 number to ofloxacin is in line with our results, the incidence in our study is higher.

The pathophysiological mechanism underlying 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 ischemic process (16). Other authors have considered the tendon disorders to be caused by a toxic effect on collagen fibres (17). Furthermore, the 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. The number of patients with tendinitis in our study is relatively small, and the follow-up is limited to only two 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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CHAPTER 6

FLUOROQUINOLONES AND THE RISK OF ACHILLES TENDON DISORDERS

ABSTRACT

Introduction

Although many case reports have been published on fluoroquinolones and Achilles tendinitis or tendon rupture, the epidemiological evidence is scanty. We performed a nested case-control study among a cohort of users of fluoroquinolones in a large general practitioners' database in order to investigate the association with Achilles tendon disorders.

Methods

Data came from the United Kingdom Mediplus database which consists of all data on consultations, morbidity, prescriptions, and other interventions, as registered by general practitioners in a source population of approximately 1-2 million inhabitants. The cohort included 46,776 persons aged 18 to 95, who had received at least one prescription of a fluoroquinolone in the period between July 1, 1992 and June 30, 1998. Potential cases were identified by the registration of Achilles tendinitis or Achilles tendon rupture. Patients with a history of tendinitis or tendon rupture, with a preceding trauma, or with an inadequate diagnosis, were excluded on the basis of a review of the patient profiles and additional clinical data, blinded as to the exposure status. A group of 10,000 control patients were randomly sampled from the study cohort, with a random date included in the follow-up period of that individual taken as index date.

Results

We identified 742 patients with Achilles tendon disorders of whom 704 had an Achilles tendinitis and 38 had an Achilles tendon rupture. The estimated incidence rate (per 1,000 person years) of Achilles tendon disorders was 7.2 (95%CI: 5.3-9.6) during the use of any fluoroquinolone, as compared to 3.0 (95%CI: 2.8-3.2) during non-use (RR = 2.4 (1.8-3.3)). In the nested case-control analysis, the adjusted relative risk of Achilles tendon disorders following current use of fluoroquinolones was 1.9 (95%CI: 1.3-2.6). Among patients of 60 years and older, the relative risk was 3.2 (95%CI: 2.1-4.9) as against 0.9 (95%CI: 0.5-1.6) among patients younger than 60. In the elderly, the relative risk was 11.5 (95%CI: 5.2-25.7) for current use of ofloxacin, while the relative risks were 2.3 (95%CI: 1.4-4.0) and 1.8 (95%CI: 0.4-8.0) for ciprofloxacin and norfloxacin, respectively. In patients of 60 years and older, concurrent use of corticosteroids and fluoroquinolones increased the risk to 6.2 (95%CI: 3.0-12.8)

Conclusion

Current use of fluoroquinolones increased the risk of Achilles tendon disorders, especially among elderly who were treated with concomitant use of corticosteroids. In clinical situations in which there are no antibacterial therapeutic alternatives, fluoroquinolones other than ofloxacin might be preferred in this group of patients.

INTRODUCTION

Fluoroquinolones are a relatively new class of antibacterial agents that act by inhibiting bacterial DNA gyrase. These drugs are among the most frequently prescribed antibacterial agents due to their broad spectrum, relatively few serious adverse reactions, and good oral absorption (1, 2). The recent approval of fluoroquinolones with a broader antibacterial spectrum and the possibility of once daily dosing may lead to an even more frequent use of these drugs (3).

Since their introduction fluoroquinolones have been associated with reports of tendinitis (4, 5). During the past years, the number of reports has risen, possibly because of the increased use of fluoroquinolones (6-12). In the vast majority of cases, the Achilles tendon was affected with symptoms compatible with painful tendinitis or with rupture, usually during the first month of treatment. Although many case reports have been published, the epidemiological evidence is scanty. In a follow-up study, we previously reported on an elevated risk of tendinitis, especially Achilles tendinitis to fluoroquinolones (13). In that study, the relative risk was highest for ofloxacin. However, the number of cases was small and the follow-up was limited to 2 years. Therefore, we performed a nested case-control study among users of fluoroquinolones in a large UK general-practitioner database to study the association with Achilles tendon disorders and its determinants.

METHODS

Setting

Data for this study were obtained from the IMS HEALTH United Kingdom Primary Care Database (UK *MediPlus*®). This system contains general practice patient records which are collected from around 160 computerised practices (Torex Medical System 5) throughout the UK. The database contains demographic information, patient complaints, symptoms, laboratory tests, diagnoses, hospital referrals, and prescription details (including drug name, dosage form, dose, quantity prescribed, and indication), from a source population of approximately 2 million inhabitants (1 million patients currently registered). The Read coding system is used to code patient complaints, diagnoses, and prescribed drugs and their indications. For research purposes the Read codes were mapped onto ICD-9 codes. Anonymized data from participating practices are collected by IMS-HEALTH via a modem on a daily basis. The regional distribution of practices and doctors is representative of the United Kingdom as a

whole, except that there is a higher proportion of younger physicians and an under-representation of practices in Scotland, Northern Ireland and Wales. For this study, data were used from 135 practices during the period between July 1, 1992 and June 30, 1998.

Study population

The study population consisted of all patients of 18 years and older with a permanent registration status, who received at least one prescription for any of the following fluoroquinolones during the study period: ciprofloxacin, norfloxacin, ofloxacin, cinoxacin, enoxacin, and temafloxacin. In order to be included, patients needed to have at least 18 months of information on drugs prescribed and diagnoses recorded on computer prior to the date of diagnosis. Persons with a history of Achilles tendon disorders, cancer, AIDS, illicit drug abuse, or alcohol abuse before the beginning of the study period were excluded. A total of 46,776 persons formed the final study cohort and were followed from the date at which each cohort member had 18 months of medical history until the occurrence of an Achilles tendon disorder, death, one of the exclusion criteria (as defined above), a transfer out of the study region, or the end of the study period, whichever event occurred earliest.

Cases

For all 867 patients with a first time registration of Achilles tendon disorders during the study period, a patient profile was generated including GP medical diagnoses, laboratory results, and hospital referrals, plus all prescriptions except for the study drugs, to warrant unbiased review. Upon review of these patient profiles, 125 patients were excluded because of trauma in the 3 months prior to the diagnosis of Achilles tendon disorders, or because the diagnosis was inadequate (e.g. bursitis). For the remaining 742 cases, the date of diagnosis of an Achilles tendon disorder was defined as the index date.

Cohort-analysis

Incidence rates for tendon disorders during the non-exposed period and the exposed period were calculated, using cases as numerator and person-time as denominator. For each fluoroquinolone prescription, the length was calculated as the amount of prescribed drug divided by the daily dose. The risk window was defined as the length of a fluoroquinolone prescription and the first 30 days thereafter. The crude relative risk (RR) of tendon disorders was calculated by dividing the incidence rates during the exposed period by the incidence rate

during the non-exposed period. Adjusted estimates of relatives risks and corresponding ninety-five percent confidence intervals (95% CIs) were computed using a Poisson regression model with age, gender, and calendar year included in the model.

Nested case-control analysis

To evaluate potential risk factors and dose and duration effects, we performed a nested case-control analysis within the study cohort. A group of 10,000 control patients were randomly sampled from the study cohort, with a random date included in the follow-up period of that individual taken as index date. Exclusion criteria were applied equally to controls as to cases.

In order to explore the effect of both short-term and delayed effects of fluoroquinolones, we defined four exposure categories: current use, recent use, past use and non-use. A person was defined as a current fluoroquinolone user when the index date fell within the period between the start of the fluoroquinolone treatment and the calculated end date plus 30 days. A person was defined as a recent fluoroquinolone user when the index date did not fall in the current use period, and the end of the calculated legend duration was less than 90 days before the index date. A person was defined as a past user when the end of the calculated legend duration was more than 90 days and less than 18 months days before the index date. Non-users were defined as persons who did not use any of the study drugs in the 18 months preceding the index date. To find evidence for a dose-response relationship we assigned the current users to any of the 3 dose categories: < 1 defined daily dose equivalent (DDD_{eq}), 1 DDD_{eq} and > 1 DDD_{eq}. The defined daily dose (DDD) is a standardised dosing unit which was defined by the World Health Organisation as the recommended daily dose of the drug for the main indication in an adult (14). DDD_{eq} were calculated as the actually prescribed daily dose of the current prescription divided by the DDD of the prescribed fluoroquinolone. Duration of use was assessed in current users and defined as the number of days of continuous fluoroquinolone therapy.

Several potential risk factors for tendon disorders were identified through the computerised records. These included kidney transplantation, end-stage renal failure, hemodialysis, rheumatoid arthritis, osteoarthritis, gout, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, Reiter's syndrome, polymyalgia rheumatica, ulcerative colitis, Crohn's disease, diabetes mellitus, and oral corticosteroid use. Unconditional logistic regression analysis was used to estimate the crude and adjusted relative risks and 95% confidence intervals (95%CI) for Achilles tendon disorders within each category of exposure to

fluoroquinolones, using the non-user group as the reference. Attributable risk (AR) proportions were calculated with the formula AR=(RR-1)/RR. These give the percentage of Achilles tendon disorders in exposed patients which can be attributed to fluoroquinolones (15, 16).

RESULTS

The study population comprised 46,776 patients who filled 71,227 prescriptions for a fluoroquinolone. We identified 742 cases of Achilles tendon disorders; 704 patients had an Achilles tendinitis, and 38 patients had an Achilles tendon rupture. The estimated incidence rate (per 1,000 person years) of Achilles tendon disorders was 7.2 (95%CI: 5.3-9.6) during use of any fluoroquinolone, as compared to 3.0 (95%CI: 2.8-3.2) during non-use. After adjustment for age, gender, and calendar year, the RR of tendon disorders following the use of fluoroquinolones was 2.3 (95% CI: 1.7–3.1) as compared to non-use. The incidence rates during current use of individual fluoroquinolones were 12.0 (95%CI: 6.4-20.4) per 1,000 person years for ofloxacin, 6.4 (95%CI: 4.3-9.2) for ciprofloxacin, and 5.2 (95%CI: 1.4-13.5) for norfloxacin (Table 1).

Table 1
Incidence rates of and relative risks of Achilles tendon disorders for individual fluoroquinolones

	Person-years	Cases	IR/10^3	RR_{crude}	(95% CI)	$RR_{adjusted}$	(95% CI)*
Non-users	233,916	696	3.0	1.0		1.0	
Current users	6,410	46	7.2	**2.4**	**(1.8 – 3.3)**	**2.3**	**(1.7 – 3.1)**
Onoxacin	3	-	-	-		-	
Ofloxacin	1,088	13	12.0	**4.0**	**(2.3-6.9)**	**4.0**	**(2.3 – 6.9)**
Ciprofloxacin	4,538	29	6.4	**2.1**	**(1.5-3.1)**	**2.0**	**(1.4 – 2.9)**
Enoxacin	2	-	-	-		-	
Temafloxacin	1	-	-	-		-	
Norfloxacin	776	4	5.2	1.7	(0.6-4.6)	1.7	(0.6 – 4.6)
Levofloxacin	1	-	-	-		-	

* Age, gender and calendar year were included in the Poisson regression model

Table 2 shows the characteristics of cases and controls. Of the cases, 61 percent was female and the mean age was 56 years (SD: 15.5). The cases had significantly more GP-visits than the controls (mean 20 vs 17). Cases and controls were similar with respect to the indications for use. Age, number of GP-visits in the past 18 months, gout, obesity and corticosteroid use were

Table 2
Characteristics of cases and controls

	Cases (%) (n=742)		Controls (%) (n=10,000)			
	N	(%)	N	(%)	RR*	(95% CI)
Sex						
Male	289	(38.9)	3,889	(38.9)	1.00	Reference
Female	453	(61.1)	6,111	(61.1)	1.00	(0.9 – 1.2)
Age						
Mean	55.6		53.4			
18-39	130	(17.5)	2,691	(26.9)	1.00	Reference
40-59	293	(39.5)	3,367	(33.7)	**1.80**	**(1.5 – 2.2)**
60-79	278	(37.5)	3,132	(31.3)	**1.84**	**(1.5 – 2.3)**
80+	41	(5.5)	810	(8.1)	1.05	(0.7 – 1.5)
Corticosteroid exposure						
None	599	(80.7)	8,777	(87.8)	1.00	Reference
Current	34	(4.6)	247	(2.5)	**2.02**	**(1.4 – 2.9)**
Recent	35	(4.7)	265	(2.7)	**1.93**	**(1.3 – 2.8)**
Past	74	(10.0)	711	(7.1)	**1.52**	**(1.2 – 2.0)**
GP-visits (0-545 days)						
Mean	20		17			
0-5	82	(11.1)	1,547	(15.5)	1.00	Reference
5-15	201	(27.1)	3,122	(31.2)	1.21	(0.9 – 1.6)
15+	459	(61.9)	5,331	(53.3)	**1.62**	**(1.3 – 2.1)**
History of musculoskeletal related disorders						
Osteoarthritis	163	(21.7)	1,488	(14.9)	**1.61**	**(1.3 – 1.9)**
Auto immune arthritis	17	(2.3)	226	(2.2)	1.04	(0.6 – 1.7)
Spondyloarthropaties	13	(1.8)	124	(1.2)	1.42	(0.8 – 2.5)
Gout	32	(4.3)	273	(2.7)	**1.61**	**(1.1 – 2.3)**
Inflammatory bowel disease	7	(0.9)	143	(1.4)	0.66	(0.3 – 1.4)
Diabetes	40	(5.3)	540	(5.4)	1.00	(0.7 – 1.4)
Renal failure	2	(0.3)	44	(0.4)	0.61	(0.1 – 2.5)
Disorders of lipid metabolism	20	(2.7)	217	(2.2)	1.25	(0.8 – 2.0)
Obesitas	43	(5.8)	353	(3.5)	**1.68**	**(1.2 – 2.3)**
Psoriasis	30	(4.0)	293	(2.9)	1.40	(0.9 – 2.0)

* all relative risks are unadjusted

Table 3
Relative risk of Achilles tendon disorders associated with fluoroquinolone use

	Cases	Controls	RR_{crude} (95% CI)		$RR_{adjusted}$ (95% CI)*	
All tendon disorders (n = 742)						
Non-use	519	7,184	1.0		1.0	
Current use	46	298	**2.1**	**(1.5 - 3.0)**	**1.9**	**(1.3 – 2.6)**
Recent use	34	422	1.1	(0.8 - 1.6)	1.00	(0.7 – 1.4)
Past use	143	2,096	0.9	(0.8 - 1.1)	0.9	(0.7 – 1.1)
Tendon rupture (n = 38)						
Non-use	26	7,184	1.0		1.0	
Current use	3	298	2.8	(0.8 - 9.2)	2.0	(0.6 – 7.0)
Recent use	2	422	1.3	(0.3 - 5.5)	1.1	(0.3 – 5.0)
Past use	7	2096	0.9	(0.4 - 2.1)	0.9	(0.4 – 2.1)
Tendinitis (n = 704)						
Non-use	493	7,184	1.0		1.0	
Current use	43	298	**2.1**	**(1.5 - 2.9)**	**1.9**	**(1.3 – 2.6)**
Recent use	32	422	1.1	(0.8 - 1.6)	1.0	(0.7 – 1.5)
Past use	136	2096	1.0	(0.8 - 1.2)	0.9	(0.7 – 1.1)

* adjusted for gender, age, GP-visits, calendar year, corticosteroid use, history of musculoskeletal disorders, and obesitas

independent determinants of Achilles tendon disorders. Of the musculoskeletal disorders, osteoarthritis and gout were significantly associated with Achilles tendon disorders.

The adjusted relative risk of Achilles tendon disorders following current use of fluoroquinolones was 1.9 (95%CI: 1.3-2.6), while the risk for recent and past fluoroquinolone use was similar to the risk in non-users. Although not significant, the relative risk of Achilles tendon rupture was approximately of the same magnitude as the relative risk of Achilles tendinitis (Table 3).

The effect of fluoroquinolones on the occurrence of Achilles tendon disorders was modified by age. The relative risk was 3.2 (2.1-4.9) among patients of 60 years and older and 0.9 (0.5-1.6) among patients younger than 60 years (Table 4). The attributable risk proportion of Achilles tendon disorders among currently exposed elderly was 68 percent. Since the effect of fluoroquinolones seemed restricted to elderly, people further analyses were conducted only for the subset of patients of 60 years and older.

Table 4

Relative risk of Achilles tendon disorders associated with fluoroquinolone use according to age

	Cases	Controls	$RR_{adjusted}$	(95% CI)*
< 60 years of age	(n=423)	(n=6,058)		
Non-use	308	4,387	1.0	
Current use	13	174	0.9	(0.5 – 1.6)
Recent use	19	240	1.0	(0.6 – 1.7)
Past use	83	1257	0.9	(0.7 – 1.1)
≥ 60 years of age	(n=319)	(n=3,942)		
Non use	211	2,797	1.0	
Current use	33	124	**3.2**	**(2.1 – 4.9)**
Recent use	15	182	1.0	(0.6 – 1.7)
Past use	60	839	0.8	(0.6 – 1.1)

*adjusted for gender, age, GP-visits, calendar year, corticosteroid use, history of musculoskeletal disorders, and obesitas

The relative risk of tendon disorders was not homogeneous between individual fluoroquinolones (Table 5). The relative risk was 11.5 (95%CI: 5.2-25.7) for current use of ofloxacin, while the relative risks of tendon disorders were 2.3 (95%CI: 1.4-4.0) and 1.8 (95%CI: 0.4-8.0) for ciprofloxacin and norfloxacin, respectively. We could not explore an effect of dosage and duration since there was little variation in the average daily dose, and almost all courses were given

for similar short periods of time. Stratification of patients taking fluoroquinolones into those who received 1 or 2 or more prescriptions prior to the index date resulted in comparable relative risks.

Among patients of 60 years and older, corticosteroid use modified the effect of fluoroquinolones on the occurrence of Achilles tendon disorders. The relative risk of Achilles tendon disorders associated with current fluoroquinolone use was 2.3 (95%CI: 1.3-4.0) in patients not using corticosteroids, and 6.2 (95%CI: 3.0-12.8) in patients using corticosteroids (Table 6). The proportion of Achilles tendon disorders among subjects with both risk factors that is attributable to their interaction was 87 percent.

Table 5

Relative risk of Achilles tendon disorders associated with individual fluoroquinolones among patients of 60 years or older

	Cases	Controls	$RR_{adjusted}$ (95% CI)*	
Non-use	211	2,797	1.0	
Ofloxacin	13	14	**11.5**	**(5.2 – 25.7)**
Ciprofloxacin	18	96	**2.3**	**(1.4 – 4.0)**
Norfloxacin	2	14	1.8	(0.4 – 8.0)

*adjusted for gender, age, GP-visits, calendar year, corticosteroid use, history of musculoskeletal disorders, and obesitas

Table 6

Relative risk of Achilles tendon disorders associated with fluoroquinolone use among patients 60 years or older according to exposure of corticosteroids

	Cases	Controls	$RR_{adjusted}$ (95% CI)*
No corticosteroid use	(n=232)	(n=3,480)	
No fluoroquinolone use	170	2,398	1.0
Current use	16	96	**2.3 (1.3 – 4.0)**
Recent use	8	132	0.8 (0.4 – 1.7)
Past use	38	622	0.8 (0.6 – 1.1)
Corticosteroid use	(n=87)	(n=694)	
No fluoroquinolone use	41	399	1.0
Current use	17	28	**6.2 (3.0 – 12.8)**
Recent use	7	50	1.3 (0.6 – 3.2)
Past use	22	217	0.9 (0.5 – 1.6)

*adjusted for gender, age, GP-visits, calendar year, history of musculoskeletal disorders, and obesitas

DISCUSSION

This study showed that the use of fluoroquinolones is independently associated with an increased risk of Achilles tendinitis and rupture, but also that this adverse effect is relatively rare with an overall excess risk of 3.2 cases per 1,000 person-years. The effect appears to be restricted to persons of 60 years or older, and within this group concomitant use of corticosteroids increased the risk substantially. When we compared individual fluoroquinolones with non-use, we observed heterogeneity among the fluoroquinolones. The relative risk was highest for ofloxacin with an excess risk of 9 cases per 1000 person-years. We did not find any other risk factor in users of ofloxacin that could account for this increased risk. However, this finding is consistent with data from an earlier study, case series, case reports, and animal toxicity testing, which showed that ofloxacin was associated with a higher risk of tendon disorders than other fluoroquinolones, with the exception of pefloxacin

The incidence of tendinitis in this study is lower than in the Netherlands, where the incidence rate of tendinitis to fluoroquinolones was estimated at 29 per 1,000 person-years at risk. In a study, done in the French spontaneous reporting system, the estimated frequency of tendon disorders among fluoroquinolones was 20 per 100,000 prescriptions (9). Others found a frequency of 6 per 10,000 patients (17). In a study conducted in San Diego, no cases of Achilles tendon rupture were found in 2,122 ciprofloxacin-treated patients (18).

Several case series have reported that age above 60, concomitant corticosteroid use, and end-stage renal disease are risk factors for fluoroquinolone-induced tendon disorders (8, 9, 11, 19). In our study, renal failure was not associated with Achilles tendon disorders, and none of the cases had been treated by dialysis or had undergone a renal transplantation. Age appeared to be an important effect modifier of the risk of Achilles tendon disorders. There was a threefold increase in risk of Achilles tendon disorders associated with the use of fluoroquinolones among patients over 60 years of age, while there was no increased risk in patient below 60 years of age. Furthermore, use of oral corticosteroids was an important effect modifier in patients over 60 years of age.

Some potential limitations should be considered in the interpretation of our results, i.e. confounding and bias. The association between fluoroquinolone use and Achilles tendon disorders could be confounded if fluoroquinolones were prescribed to patients who were already at an increased risk of Achilles tendon disorders. The extent of this seemed limited since adjustment for potential risk

factors such as history of musculoskeletal disorders, gout, obesity and diabetes did not change the estimate considerably. Recall bias can be excluded since data on drug use were recorded on computer files before the onset of disease. During the nineties, there has been an increase in case reports implicating that fluoroquinolones may cause tendon disorders. As a consequence, physicians may diagnose Achilles tendon disorders more readily in patients currently using fluoroquinolones. If present, this diagnostic suspicion bias might partly explain the observed increase in relative risk, but then it should differ over the different calendar years. Adjustment for calendar year did not change the relative risk, so we assume that diagnostic bias did not play a major role. Moreover, a spurious association by diagnostic suspicion bias does not explain the large difference in relative risks between the individual fluoroquinolones. Since we did not have access to the original records, tendon disorders may have been misclassified despite extensive review of the computerised patient records. As the review was blinded to exposure to fluoroquinolones, however, any misclassification was unbiased and thus leading to a conservative estimate rather than to an overestimation of the risk of Achilles tendon disorders to fluoroquinolones. Confounding by indication in this study is not very likely, as the indications for fluoroquinolone use were similar between cases and controls. Furthermore, respiratory- and urinary tract infections, the main indications for fluoroquinolones, are not known as risk factors for Achilles tendon disorders.

The mechanism of tendon disorders induced by fluoroquinolones is not well understood. Fluoroquinolone induced arthropathy, however, has been described in various juvenile animal species after long-term, high-dose administration of fluoroquinolones (20, 21). Therefore, most fluoroquinolones are contraindicated in children. A Japanese group succeeded to produce fluoroquinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin, but not in adult rats (22). The sudden onset of some tendinopathies, occasionally after a single dose of a fluoroquinolone, suggests a direct toxic effect on collagen fibres (23).

In conclusion, our data confirm that exposure to fluoroquinolones increases the risk of Achilles tendon disorders, in particular among elderly who concomitantly use corticosteroids. The risk for ofloxacin was substantially higher than for the other fluoroquinolones. Prescribers should be aware of this risk, especially in elderly on corticosteroids. In clinical situations that require the prescription of a fluoroquinolone, compounds other than ofloxacin might be preferred in this group of patients.

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CHAPTER 7

FLUOROQUINOLONES INCREASE THE RISK OF ACHILLES TENDON RUPTURE

ABSTRACT

Introduction

In several case-reports, the occurrence of Achilles tendon rupture has been attributed to the use of fluoroquinolones. Since the epidemiological evidence for this association is scanty, we conducted a study to estimate the risk of Achilles tendon rupture following the use of fluoroquinolones.

Methods

We conducted a population-based case control study in the General Practice Research Database (GPRD) in the UK during the period 1988-1998. 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 prior to the index date. We excluded all persons with preceding trauma or with an inadequate diagnosis on the basis of a review of the patient profiles. 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 a total of 1,367 cases that met the inclusion criteria. The adjusted relative risk for Achilles tendon rupture was 4.2 (95%CI: 2.3-7.6) for current exposure to fluoroquinolones, 2.0 (95%CI: 1.5-3.5) for recent exposure; and 1.3 (95%CI: 0.9-2.0) for past exposure as compared to non-exposure. The relative risk of Achilles tendon rupture was 6.4 (95%CI: 3.0-13.7) in patients of 60-79 years; 20.4 (95%CI: 4.6-90.1) in patients ≥ 80 years of age; while among patients younger than 60 there were no currently exposed cases to fluoroquinolones. In persons of 60 years and older, the relative risk was 27.7 (95%CI: 6.9-111.2) for current exposure to ofloxacin; while the relative risk estimates were 3.4 (95%CI:1.3-8.8) and 12.6 (95%CI:1.4-8.8) for ciprofloxacin and norfloxacin, respectively. Concomitant use of oral corticosteroids increased the overall risk to 14.5 (95%CI:5.9-36.6).

Conclusion

Current exposure to fluoroquinolones increased the risk of Achilles tendon rupture, especially among elderly patients who were concomitantly treated with corticosteroids. In clinical situations in which there are no therapeutic alternatives, fluoroquinolones other than ofloxacin might be preferred in this group of patients.

INTRODUCTION

Since their introduction in the mid-eighties, fluoroquinolones 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 fluoroquinolones (5-8). Rupture of the Achilles tendon is a serious condition that often requires surgical treatment. Despite the fact that several case reports and case series have suggested that fluoroquinolones are causative, we are not aware of epidemiological studies on the association between fluoroquinolones and Achilles tendon rupture.

Fluoroquinolones are antibacterial agents that act by inhibiting bacterial DNA gyrase (9). These drugs are among the most frequently prescribed antibacterial agents due to their broad spectrum, relatively few serious adverse reactions, and good oral absorption (10, 11). The recent approval of fluoroquinolones with a broader antibacterial spectrum and the possibility of once daily dosing may lead to an even more frequent use of these drugs (12).

We conducted a population-based case control study using the computerised records from the General Practice Research Database to quantify the risk of Achilles tendon rupture from fluoroquinolones, 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 computerised medical information of approximately 8 million inhabitants in the United Kingdom. All information is recorded on an ongoing daily basis by general practitioners who use office computers provided by In Practice Systems (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. Data recorded include patient demographics, symptoms, diagnoses, referrals, hospitalisations, and vital status. Referral letters from consultants and hospital records are kept by the general practitioner in a manual file. The general practitioner generates prescriptions directly from the computer, thus ensuring automatic recording. A modification of the Oxford Medical Information System (OXMIS) 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 GPRD is of high quality and adequate for drug safety studies (13, 14).

Selection of cases and controls

The study population consisted of all subjects aged 18-95 years with permanent registration status at the index date (defined below) and 18 months of up to standard history. During the study period (January 1st , 1988 – January 1st , 1999), we identified all subjects who had a first-time occurrence of a potential Achilles tendon rupture (OXMIS: 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 prior to the index date. For the remaining potential cases the medical history was reviewed, blinded to drug exposure. We excluded cases if the diagnosis was other than Achilles tendon rupture (e.g. bursitis, Achilles tendinitis without rupture), or if the rupture was due to trauma. 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 controls.

Exposure definition

For each subject we identified exposure to fluoroquinolones prior to the index date. Exposure was categorised in 3 mutually exclusive categories based on the time since the last exposure. A person was classified as currently exposed to fluoroquinolone if the index date fell within the period between the start of the fluoroquinolone treatment and the prescription length plus 30 days. A person was classified as recently exposed to fluoroquinolone 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 as non-exposed.

To study a dose-effect relationship, the prescribed daily dose (PDD) was expressed in defined daily dose (DDD) equivalents in order to be able to proxy the effect of equipotent doses of all fluoroquinolones on the occurrence of

Achilles tendon rupture. The DDD is a standardised dosing unit which represents the average daily dose for an adult for the main indication (15). The PDD/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 fluoroquinolone 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's syndrome, polymyalgia rheumatica, ulcerative colitis, Crohn's disease, diabetes mellitus and systemic corticosteroid use (16-25). The presence of these risk factors was obtained from the computerised patient records. As an additional potential confounder, we assessed the number of GP-visits in the 1.5 years prior to the index date.

Analysis

Relative risks were estimated by odds ratios. Unconditional logistic regression analysis was used to determine the crude and adjusted relative risks and 95% confidence intervals (95%CI) for Achilles tendon rupture within each category of exposure to fluoroquinolones, using the non-exposed group as the reference. Similarly, we calculated univariate relative risks for all other potential risk factors. Subsequently, multivariate logistic regression models were used to adjust for age, gender, 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 known risk factors unless they were not univariately associated (at a $p<0.10$) in our study with Achilles tendon rupture. In addition we conducted stratified analyses by age, gender, and concomitant use of corticosteroids, to identify potential effect modification. Attributable risk proportions were calculated, using the formula $AR=p(RR-1)/\{1+p(RR-1)\}$. All analyses were conducted using SPSS 9.0.

Table 1
Characteristics of cases and controls

	Cases (n = 1,367)		Controls (n = 50,000)			
	N	%	N	%	RR*	(95% CI)
Sex						
Female	418	(30.6)	26,014	(52.0)	1.0	Reference
Male	949	(69.4)	23,986	(48.0)	**2.5**	**(2.2-2.8)**
Age						
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)	2,614	(5.2)	0.7	(0.5-1.0)
Calendar Year						
1989-1990	22	(1.6)	1,265	(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)	7,914	(15.8)	**1.8**	**(1.2-2.8)**
GP-visits (0-545 days)						
Mean	12		14			
0-5	529	(38.7)	20,657	(41.3)	1.0	Reference
6-15	480	(35.1)	17,428	(34.9)	1.1	(0.9-1.2)
> 15	358	(26.2)	11,915	(23.8)	**1.2**	**(1.0-1.3)**
Corticosteroid use	154	(11.3)	2,291	(4.6)	**2.6**	**(2.2-3.1)**
History of musculoskeletal Related disorders						
Osteoarthrosis	103	(7.5)	3,035	(6.1)	**1.3**	**(1.0-1.5)**
Auto immune arthritis	95	(6.9)	2,833	(5.7)	**1.2**	**(1.0-1.5)**
Spondyloarthropathies	7	(0.5)	232	(0.5)	1.1	(0.5-2.3)
Non articular 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)	1,202	(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)	1,441	(2.9)	1.1	(0.8-1.5)
Psoriasis	27	(2.0)	1,054	(2.1)	0.9	(0.6-1.4)

* all relative risks in this table are unadjusted

RESULTS

We initially identified 1,528 potential cases of Achilles tendon rupture during the study period. Of these, 100 patients were excluded by the computer-based algorithms due to the presence of one of the exclusion criteria. Following blinded review of the remaining 1,428 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 rupture (tendinitis, bursitis, rupture of other tendon). Consequently, 1,367 cases were included in our study.

Table 1 shows the demographic and medical characteristics of cases and controls. Of the cases, 69 percent were male, and the mean age was 48 years. Cases and controls were similar with respect to the number of GP-visits and the mean age; but when stratified, there were slight differences. 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, rheumatoid arthritis, and gout, were significantly associated with Achilles tendon rupture. A history of tendinitis was strongly associated with Achilles tendon rupture (Table 1).

Exposure to any of the fluoroquinolones in the 18 months before the index date was observed in 4.5 percent and 2.0 percent of the cases and the controls, respectively. The adjusted relative risk for Achilles tendon rupture was 4.2 (95%CI: 2.3-7.6) for current exposure to fluoroquinolones; 2.3 (95%CI: 1.5-3.5) for recent exposure; and 1.3 (95%CI: 0.9-2.0) for past exposure as compared to non-exposure (Table 2).

The effect of fluoroquinolones on the occurrence of Achilles tendon rupture was not modified by gender, whereas age appeared to be a strong modifier of the effect. The relative risk of Achilles tendon rupture was 6.4 (95%CI: 3.0-13.7) in patients of 60-79 years; 20.4 (95%CI: 4.6-90.1) in patients ≥ 80 years of age; whereas among patients younger than 60, there were no currently exposed cases to fluoroquinolones (Table 2). Since the effect of fluoroquinolones seemed more pronounced in elderly people, whereas the exposure was low among younger persons, further analyses were conducted only for the subset of patients of 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 > 1.25 DDD-equivalent per day (Table 3). Duration of use of fluoroquinolones had little influence on the risk of Achilles tendon rupture, since almost all courses were given for similar short periods of time.

Table 2

Risk of Achilles tendon rupture associated with fluoroquinolones

	Cases	Controls	RR_{crude}	$RR_{adjusted}$ #	(95% CI)
Fluoroquinolones	(N = 1,367)	(N = 50,000)			
Non-use	1305	48,981	1.0	1.0	Reference
Current use (0-1 month)	14	100	**5.3**	**4.2**	**(2.3-7.6)**
Recent use (2-6 months)	24	314	**2.9**	**2.3**	**(1.5-3.5)**
past use (7-18 months)	24	605	1.5	1.3	(0.9-2.0)
< 60 years of age					
No fluoroquinolone exposure	1,029	36,373	1.0	1.0	Reference
Current fluoroquinolone exposure	-	50	-	-	-
60 – 79 years					
No fluoroquinolone exposure	243	10,093	1.0	1.0	Reference
Current fluoroquinolone exposure	11	41	**11.1**	**6.4**	**(3.0-13.7)**
≥ 80 years of age					
No fluoroquinolone exposure	33	2,515	1.0	1.0	Reference
Current fluoroquinolone exposure	3	9	**25.4**	**20.4**	**(4.6-90.1)**

adjusted for age, gender, corticosteroid use, musculoskeletal related disorders, disorders of lipid metabolism, and transplants or dialysis

Table 3

Risk of Achilles tendon rupture associated with individual fluoroquinolones and according to dose among patients of 60 or older

	Cases	Controls	RR_{crude}	$RR_{adjusted}$ #	(95% CI)
Fluoroquinolones					
Non-use	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)**
Prescribed daily dose					
Non-use	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)**

adjusted for age, gender, corticosteroid use, musculoskeletal related disorders, disorders of lipid metabolism, and transplants or dialysis

Table 4.

Current fluoroquinolone exposure among patients of 60 years and older stratified for concurrent exposure to oral corticosteroids

	Cases	Controls	RR_{crude}	$RR_{adjusted}$ #	(95% CI)
No oral corticosteroids					
No fluoroquinolone exposure	228	11,877	1.0	1.0	Reference
Current fluoroquinolone exposure	4	39	**5.3**	**5.3**	**(1.8-15.2)**
Current exposure to oral corticosteroids					
No fluoroquinolone exposure	24	194	1.0	1.0	Reference
Current fluoroquinolone exposure	9	5	**14.6**	**17.5**	**(5.0-60.9)**
Recent exposure to oral corticosteroids					
No fluoroquinolone exposure	14	263	1.0	1.0	Reference
Current fluoroquinolone exposure	1	2	9.4	**18.4**	**(1.4-240.2)**
Past exposure to oral corticosteroids					
No fluoroquinolone exposure	10	274	1.0	1.0	Reference
Current fluoroquinolone exposure	-	4	-	-	-

adjusted for age, gender, musculoskeletal related disorders, disorders of lipid metabolism, and transplants or dialysis

Although we observed heterogeneity of the risk between the different fluoroquinolones, the confidence intervals overlapped. The relative risk of Achilles tendon rupture was 28.4 (95%CI: 7.0-115.3) for current exposure to ofloxacin; while the relative risk estimates were 3.6 (95%CI:1.4-9.1) and 14.2 (95%CI:1.6-128.6) for ciprofloxacin and norfloxacin, respectively (Table 3). Concomitant use of fluoroquinolones with oral corticosteroids modified the risk of Achilles tendon rupture. The relative risk of Achilles tendon disorders associated with current exposure to fluoroquinolones was 5.3 (95%CI: 1.9-15.1) in patients not using oral corticosteroids, and 17.5 (95%CI: 5.0-60.9) respectively 18.4 (95%CI: 1.4-240.2) in patients with current and recent exposure to oral corticosteroids (Table 4). Since parenteral corticosteroids are often used to treat tendinitis, we excluded these from the analyses.

The population attributable risk percentage in patients of 60-79 years was calculated at 2.2%, while this percentage was 6.3 in people of ≥ 80 years.

DISCUSSION

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 fluoroquinolones was independently associated with an increased risk of Achilles tendon rupture. This effect was only demonstrated in persons of 60 years or older; and within this group concomitant use of corticosteroids did increase the risk substantially. These findings confirm the results from case series and case reports which suggested that age above 60 and concurrent corticosteroid use were risk factors for fluoroquinolone-induced tendon disorders (6, 26, 27).

Among the individual fluoroquinolones, the highest risk of Achilles tendon rupture was found for users of ofloxacin. Although the confidence intervals of the risk estimates overlapped those of the other fluoroquinolones, this finding is consistent with data from previous studies (28), case series (6), case reports (7, 8), and animal toxicity testing (29), which showed that ofloxacin and pefloxacin (which is not marketed in the UK) were associated with a higher risk of tendon disorders than other fluoroquinolones.

In our study, oral corticosteroid use was not only an important independent risk factor; but in combination with current exposure to fluoroquinolones, also strongly increased the risk of Achilles tendon rupture in patients over 60 years of age. 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 (16, 17, 19, 22, 25). Adjustment for these risk factors, however, did not change the risk estimate for fluoroquinolones considerably.

The incidence of Achilles tendon rupture varies among different studies, but seemed to have increased in the past few decades and shows a bimodal age distribution (30, 31). Data about the incidence of fluoroquinolone 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 (32).

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 general practitioner. 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 have been misclassified despite extensive review

of the computerised patient records. As the review was blinded to exposure to fluoroquinolones, however, any misclassification was unbiased and thus leading to a conservative estimate rather than to an overestimation of the risk of Achilles tendon rupture to fluoroquinolones. Prescription data in the General Practice Research Database are automatically registered when the general practitioner writes a prescription. These data are considered complete, which means that misclassification of fluoroquinolone use was unlikely. Recall bias can be excluded since data on drug use were recorded before the onset of disease. During the nineties, there has been an increase in case reports implicating that fluoroquinolone may cause tendon disorders. As a consequence, diagnostic suspicion bias might partly explain the observed increase in relative risk, if physicians would diagnose Achilles tendon disorders more readily in patients currently using fluoroquinolones. 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 fluoroquinolones 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.

The most important risk factor for the development of Achilles tendon rupture is probably sporting, in particular the recreational sports which demand sudden acceleration and jumping (24, 25, 33). 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 fluoroquinolones were 60 years or older; whereas the incidence of sport-related ruptures is highest between 30 and 40 years of age, while that of non-sport related ruptures peaks between 50 and 70 years of age (30, 31).

The mechanism of Achilles tendon rupture induced by fluoroquinolones is not well understood, although it is known that fluoroquinolones exhibit a pronounced affinity for connective tissues. A Japanese group succeeded in producing fluoroquinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin, but not in adult rats (29, 34). Others succeeded in providing experimental evidence of pefloxacin-induced oxidative stress in the Achilles tendon that altered proteoglycan anabolism and oxidised collagen (35). Recently, it was hypothesised that fluoroquinolones may exert their effect by disturbing the physiological interaction between cells and matrix by chelating divalent ions (36).

In conclusion, our data confirm that exposure to fluoroquinolones 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 2-6% of all Achilles tendon ruptures in people above 60 years of age can be attributed to the use of fluoroquinolones. Prescribers should be aware of this high risk and should try to avoid the combination with oral corticosteroids, or should prescribe alternative antimicrobial agents, if possible.

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CHAPTER 8

GENERAL DISCUSSION

BACKGROUND

Fluoroquinolones are antibacterial agents which act by inhibiting bacterial DNA gyrase (topoisomerase II) (1). They are particularly effective for the treatment of infections of the urinary-, respiratory-, and gastro-intestinal tract (2). In primary care, these drugs are among the most frequently prescribed antibacterial agents due to their broad spectrum, good oral absorption, and relatively few serious adverse reactions (3, 4). The most frequently observed adverse effects are of gastro-intestinal origin, followed by mild neurological disorders (headache and dizziness), and skin reactions (2, 5, 6). However, postmarketing surveillance studies have identified severe adverse events, including anaphylaxis, QTc-interval prolongation, and liver toxicity, associated with several fluoroquinolones that either resulted in the removal of the agent from the market (temafloxacin and grepafloxacin) or in the restriction of its use (trovafloxacin) (7). Since animal studies have shown that fluoroquinolones may damage juvenile joints, most fluoroquinolones are contra-indicated in children, and during pregnancy and lactation (8, 9).

In the eighties, the first representatives of this group, norfloxacin, ciprofloxacin, ofloxacin, and pefloxacin, were registered in several countries. Shortly after their introduction, however, anecdotal case reports associated the use of norfloxacin and ciprofloxacin with tendinitis (10, 11). The first case of Achilles tendon rupture in a fluoroquinolone-treated patient was published in 1991 (12). During the past years, the number of reports of fluoroquinolone-associated tendinitis with or without rupture has risen, possibly because of an increased use of fluoroquinolones (13-22). At present, more than 1,000 cases of fluoroquinolone-attributed tendon disorders have been reported to the WHO Collaborating Centre for International Drug Monitoring (23). Tendinitis and especially tendon rupture are serious injuries that may lead to substantial morbidity. Manifestations can persist for several weeks or months and may result in substantial functional impairment, especially if early manifestations did not receive appropriate attention. Tendon ruptures often require surgical treatment.

The aim of this thesis was to provide epidemiological evidence regarding the association between the use of fluoroquinolones and the occurrence of tendon disorders. The studies described were based on data from case reports, computerised pharmacy records, and general practitioner's automated databases. In this chapter, the most important findings will be summarised, methodological issues of the studies will be discussed, and clinical implications will be given. Finally, recommendations for future research will be made.

MAIN FINDINGS

Utilisation of fluoroquinolones

In the Netherlands, a large increase in use of fluoroquinolones was observed in the community during the period 1991 through 1996. The total number of DDDs per 1,000 inhabitants per day increased from 0.26 in 1991 to 0.57 in 1996. This rise in fluoroquinolone use is in line with the increased use in Canada, Germany, Italy, the UK, Spain, and the USA. To the contrary, there was a decrease in fluoroquinolone use in France and Australia after 1994, which can be ascribed to recent changes in reimbursement (24-26). Since there was no distinct increase in the rate of infections and the approved indications for fluoroquinolones did not essentially change during this period, the observed rise in use suggests that patients were more readily treated with these antibacterial agents.

Case series

Case series may be useful as a hypothesis-generating tool. Our evaluation of 42 Dutch reports of fluoroquinolone-associated tendon disorders suggested that this adverse effect occurs predominantly in patients over 60 years of age. The Achilles tendons appeared to be the most susceptible ones, although effects on tendons of the *musculus quadriceps femoris*, the epicondyles, and the rotator cuff of the shoulder, were reported as well. The disorder was bilateral in more than 50 percent of the cases which is also consistent with the literature. The latency period between the start of treatment and the onset of symptoms was usually one week, but sometimes a few months, which is in line with previous case reports (18, 19, 22). Duration of recovery was variable, and a substantial part of the cases had persistent symptoms.

Correlational studies

We also studied the potential public health effects of an association between fluoroquinolone use and tendon ruptures in the Netherlands in a correlational study. We observed a large simultaneous increase in non-traumatic tendon ruptures and fluoroquinolone use during the period between 1991 and 1996. However, assuming a variation of the relative risk from 1.5 to 10.0 for tendon ruptures during fluoroquinolone use, only 0.5 to respectively 7% of the increase

in non-traumatic tendon ruptures could be attributed to the increased fluoroquinolone use.

Observational studies

Because both the prevalence of fluoroquinolone use as well as the prevalence of Achilles tendon disorders are low, we used large automated GP-databases to study the association between fluoroquinolone use and tendon disorders in general practice. Overall, the observational studies showed that there was a strong association between fluoroquinolone use and Achilles tendinitis and Achilles tendon rupture, but also that this adverse effect was relatively rare.

In our first observational study, we used data from the Dutch Integrated Primary Care Information (IPCI) system (27) to study the association between fluoroquinolone use and all forms of tendinitis. We observed that the risk of tendinitis following use of fluoroquinolones was elevated when compared to a reference group of four commonly used antibacterial agents with a known safety profile. After stratification for type of tendinitis, we found that the risk of Achilles tendinitis during use of fluoroquinolones was four times higher than during use of the other antibacterial agents. Although we observed a slight heterogeneity among the different fluoroquinolones, suggesting that the risk was highest for ofloxacin, the study had not enough power to prove this despite the substantial size of the source population of approximately 385,000 persons in the IPCI system.

Therefore, we subsequently performed a nested case-control study in a cohort of fluoroquinolone users in the IMS HEALTH United Kingdom Primary Care Database (UK *MediPlus*®), which has a source population of 1-2 million persons. The aim of that study was to assess the risk of Achilles tendinitis or rupture during use of fluoroquinolones. We observed that current use of fluoroquinolones was associated with a twofold increase in risk of either Achilles tendinitis or rupture. The overall excess risk was 3.2 cases per 1000 person-years of fluoroquinolone use. When we compared individual fluoroquinolones to non-use, the relative risk was significantly higher for ofloxacin. This study suggested that age and concomitant oral use of corticosteroids were risk factors.

In order to explore these potential risk factors for Achilles tendon rupture, we performed a population-based case-control study in the General Practice Research Database. (28, 29). This database contains computerised medical information of approximately 4 million inhabitants in the United Kingdom. We observed that current use of fluoroquinolones was associated with a fourfold increased risk of Achilles tendon rupture. The risk was most strongly elevated in

the elderly on corticosteroids. Among the individual fluoroquinolones, the highest risk of Achilles tendon rupture was found for users of ofloxacin, but a statistically significant difference between individual fluoroquinolones could not be proven.

Risk Factors

Age

Age proved to be an important risk factor for fluoroquinolone-attributed tendon disorders. In our case series, 71 percent of the patients was over 60 years of age, and also most case reports and case series in the literature concerned patients over 60 years of age (16, 18, 19, 21, 22). From our drug utilisation study, it became apparent that use of fluoroquinolones is most prevalent among elderly. Hence, we do not know whether the risk is restricted to elderly. However, in both case-control studies presented in this thesis, age was an important effect modifier. The study which was performed in the IMS HEALTH United Kingdom Primary Care Database showed a threefold increase in risk among patients of 60 years and older, while among patients younger than 60 years no difference in risk of Achilles tendon disorders was found between current users of fluoroquinolones and non-users. In the General Practice Research Database, we found a relative risk of 6.4 among patients of 60-79 years, which increased to 20.4 in patients of 80 years and older, while among patients younger than 60 years of age there were no cases during current use of fluoroquinolones.

Corticosteroids

Although there is a strong clinical suspicion that use of oral corticosteroids may be an independent risk factor for Achilles tendon rupture, the epidemiological evidence is scanty. In the studies performed in this thesis, concomitant use of oral corticosteroids appeared to be an important effect modifier of fluoroquinolone-induced tendon disorders. Not only did 20 percent of the patients in our case series use fluoroquinolones and oral corticosteroids together but in both case-control studies presented in this thesis, concomitant oral corticosteroid use increased the risk of fluoroquinolone-induced tendon disorders considerably among elderly. The study done in the IMS HEALTH United Kingdom Primary Care Database showed that in patients of 60 years and older, concurrent use of corticosteroids and fluoroquinolones increased the risk from 2.3 (95% CI: 1.3-4.0) in users of fluoroquinolones alone to 6.2 (95% CI: 3.0-12.8) in patients using the combination. Similarly, in the General Practice Research Database we observed that in patients of 60 years and older concurrent use of corticosteroids

and fluoroquinolones increased the risk from 5.1 (95%CI: 1.9-15.1) to 17.5 (95%CI: 5.0-60.9), respectively.

Other risk factors
Besides age and corticosteroid use, we also studied other known risk factors for tendon disorders. These include organ transplantation, end-stage renal failure, hemodialysis, rheumatoid arthritis, osteoarthritis, gout, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, polymyalgia rheumatica, ulcerative colitis, Crohn's disease, and diabetes mellitus. Of these, ostheoarthrosis, inflammatory joint diseases, gout, organ transplantation, and hemodialysis were independent risk factors for Achilles tendon disorders in our studies. Adjustment for these risk factors, however, did not change the risk estimate for fluoroquinolones considerably.

METHODOLOGICAL CONSIDERATIONS

In general, three types of bias can be distinguished: selection bias, information bias and confounding. These issues will be discussed in the next paragraphs.

Selection Bias
Selection bias is a distortion of the risk estimate which results from procedures used to select subjects for the study (30). Especially in field-oriented case-control studies this type of bias may be of major concern. Since our case-control studies used all general practitioner's data from a large and complete population, selection bias is unlikely, because most cases were probably registered and the controls were randomly selected from the study base. Moreover, information concerning known risk factors was already available which eliminates the selection bias due to non-response. We cannot exclude, however, that some diagnostic bias played a role in our studies if general practitioners would more readily have diagnosed tendinitis among users of fluoroquinolones. It is unlikely that all GPs were aware of this association during the study period and that their decision to diagnose an Achilles tendon disorder would depend on this knowledge. Moreover, Achilles tendon rupture, which is not easily misclassified and therefore less vulnerable to diagnostic bias, was also strongly associated with the use of fluoroquinolones. Hence, we think that selection bias in our studies is unlikely.

Information Bias

Information bias may occur when there is random (non-differential) or systematic (differential) misclassification of either the outcome, the determinant or confounding variables (30). The possibility exists that some of the tendon disorders have been misclassified. Differential misclassification of outcome relates to diagnostic bias (see above). Non-differential misclassification of the outcome may be due to either or both false-positive and false-negative cases. False-positive misclassification is a more serious threat to the validity of the risk estimate than the false-negative misclassification since the outcome is extremely rare. Because case review was extensive and blinded to exposure to fluoroquinolones, any misclassification of outcome is probably small and non-differential. This tends to underestimate rather then overestimate the true relative risk and will lead to a conservative estimate (31).

Another important aspect is misclassification of exposure to drugs. Especially the timing and dosage of the exposure are potential sources of misclassification. The prescription data from the GP-databases which we used are considered complete and included date of prescription, drug name, dosage form, daily dose, prescribed quantity, and indication. However, patients may not have filled their prescription at the pharmacy, may have used the drugs later, or may not have taken the drugs. Moreover, because of the low prevalence of fluoroquinolone use we were not able to fully explore the relevant time window for current exposure in detail. Case reports suggest that the median latent period is two weeks. Since misclassification due to imprecise risk windows will be non-differential, it will only have reduced the strength of the association (31).

One of the advantages of studies using automated GP data is that data on disease and exposure are gathered prospectively by GPs who are not aware of the research hypothesis, and are stored automatically. Therefore recall bias does not play a role.

Confounding

Confounding occurs when a third factor (the confounder) is associated with both the exposure of interest and the outcome of interest, without being an intermediate step in the causal pathway (30, 31). A major concern in observational studies of drug effects is confounding by indication (32). In observational studies of rare idiosyncratic adverse drug reactions this is of less concern, since the indication is usually not a risk factor for the adverse reaction. To our knowledge there is no association between the indication for fluoroquinolones (mainly urinary- and respiratory tract infections) and tendon

disorders, which means that confounding by indication was not likely in our studies. This was confirmed by the fact that we found that the risk of tendinitis to fluoroquinolones was also elevated when we compared it to a reference group of four commonly used antibacterial agents (amoxicillin, trimethoprim, co-trimoxazole, and nitrofurantoin) with a known safety profile and the same indications.

BIOLOGICAL EXPLANATIONS

Case reports and the findings in our studies consistently implicated fluoroquinolone use as a risk factor to develop tendinitis and tendon rupture. It is, however, not clear through which mechanism fluoroquinolones may cause tendon disorders in humans.

Fluoroquinolones exhibit a pronounced affinity for connective tissues. Concentrations in cartilage, bone, and other tissues shortly after intake exceed those measured simultaneously in plasma (1, 2). Although no specific data are available, it is reasonable to assume that toxic levels at the site of injury may occur.

In two histopathological studies in humans (19, 33), neovascularisation, interstitial edema, and severe degenerative lesions were found, but no inflammatory cell infiltrate, which might be compatible with an ischemic process. Another study showed abnormal fibre structure and arrangement, hypercellularity, and increased interfibrillar glycosaminoglycans (34). These histopathological findings are similar to those under conditions of heavy exercise by athletes. It has been suggested that fluoroquinolones alter cellular function, creating an excess production of non-collagenous extracellular matrix and a subsequent change in cell to matrix ratio (34). Japanese researchers succeeded to reproduce fluoroquinolone-induced tendinitis in juvenile rats after high doses of pefloxacin and ofloxacin but not in adult rats (35). The fluoroquinolone-induced lesions were characterised by edema and mononuclear cell infiltration in the inner sheath of the inner Achilles tendon, with infiltration into the adjacent synovial membrane and joint space. Electron microscopic examination showed an increased number of fibroblasts, macrophages, and collagen disposition in the matrix of the synovial membrane and tendon sheath. In a subsequent study, the authors showed that out of 10 fluoroquinolones, pefloxacin, ofloxacin, and fleroxacin, were the most toxic derivatives whereas sparfloxacin, norfloxacin, and ciprofloxacin, were less toxic or produced no lesions even after rather high doses (36). These findings could, however, also be explained by the kinetics of

the compounds in rats. The absorption of fluoroquinolones from the gastrointestinal tract in rats differs considerably for various fluoroquinolones. Moreover, in this study partial reduction of the incidence of tendinopathies by pefloxacin was obtained by administration of L-NAME (N-nitro-L-arginine methyl ester, a nitric oxide synthase inhibitor). This suggests that nitric oxide partly mediates the induction of lesions, which is in agreement with the finding that formation of radicals is an important step in the pathogenesis of fluoroquinolone-induced arthropathy (9). An in vitro-study showed that the viability of rabbit tenocytes was altered by fluoroquinolones, and that this effect occurred at concentrations that are comparable to therapeutic concentrations (37). Others produced experimental evidence of pefloxacin-induced oxidative stress in the Achilles tendon which altered proteoglycan anabolism and oxidised collagen (38). Finally, it has been hypothesised that fluoroquinolones may exert their effect by disturbing the physiological interaction between cells and matrix by chelating divalent ions like magnesium (39).

CLINICAL IMPLICATIONS

Ideally, the choice to prescribe a certain antibacterial agent to treat an infection should be based on the antibacterial spectrum and on a tailored benefit/risk assessment. This means that a prescriber should be aware of the frequency of beneficial and harmful effects of the drug and know which clinical characteristics may modify the assessment. Fluoroquinolones are antibacterial agents with a broad antibacterial spectrum, good oral absorption, and relatively few serious adverse drug reactions. Unfortunately, their ease of use may promote indiscriminate intake (4). This may become a problem for the newest fluoroquinolones that possess an even broader antibacterial spectrum (many gram-positive, gram-negative and anaerobic bacteria) and a user-friendly dosing regimen.

Achilles tendinitis and Achilles tendon rupture are rare but strongly associated with fluoroquinolone therapy. Tendinitis and especially tendon rupture are serious injuries that may lead to substantial morbidity, especially if early manifestations did not receive appropriate attention. Therefore, physicians should consider a change of therapy at the first sign of a potential tendon disorder.

In a primary care environment, the risk is highest among elderly who concurrently use oral corticosteroids. Calculation of the population attributable risk among elderly suggests that up to 6% of all Achilles tendon ruptures are caused by the use of fluoroquinolones. Since fluoroquinolones are mainly

prescribed to elderly in a primary care setting, sometimes for inappropriate reasons (4, 40), a certain fraction of tendon disorders may be prevented. On the other hand, the risk may be acceptable when fluoroquinolones are prescribed for severe infections.

FURTHER RESEARCH

The studies in this thesis confirm that fluoroquinolones may cause Achilles tendinitis and Achilles tendon rupture, especially when combined with oral corticosteroids in elderly. Although the risk is probably highest for ofloxacin, we were not able to find a statistically significant difference with the other fluoroquinolones in most studies. The attributable risk may be substantial in the very old, although in this age-group the contribution of other factors to Achilles tendon rupture also prevails.

Although several animal studies have been performed, the exact mechanism of fluoroquinolone induced-tendon disorders is still unknown. More basic research is needed to identify this mechanism. Over the years, several models for structure-activity and adverse effect relationships have been developed for fluoroquinolones. Crystalluria, CNS effects, drug interactions with theophylline and NSAIDs, phototoxicity, and potential genotoxicity seemed to be sensitive to structural changes (41, 42). It might be possible to identify which part of the fluoroquinolone molecule is responsible for fluoroquinolone-induced tendon disorders, but of course the question remains whether this can be removed without loss of antibacterial activity.

Animal studies showed that magnesium depletion may play a role in the development or duration of fluoroquinolone-induced tendon disorders(39). Observational studies can yield evidence for this theory by studying the association between diseases (e.g. diabetes mellitus) or drugs (e.g. diuretics) that can cause hypomagnesia, and tendon disorders.

Although we used several of Europe's biggest healthcare databases, we did not have enough power to detect significant differences between the individual fluoroquinolones with respect to Achilles tendon rupture. The increasing availability of automated healthcare databases in various countries (Denmark, Italy) might allow future researchers to perform a multinational database study. Although this may create some variability in the type and quality of data, the large numbers might facilitate comparisons between individual drugs when studying rare adverse events. Another way to increase precision in the estimation

of rare effects to uncommonly used drugs is to conduct a nationwide case-cohort study as performed by van der Klauw et al. (43).

Development of new databases which include not only morbidity and medication but also genetic and genealogic data may be helpful to identify patients that are at increased risk for particular adverse drug reactions. In Iceland such a database is currently being developed (Icelandic Healthcare database) (44).

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CHAPTER 9

SUMMARY & SAMENVATTING

SUMMARY

The choice to prescribe a particular antibacterial agent should depend on the antibacterial spectrum and on the benefit/risk evaluation for each patient. This requires a prescriber to be aware of the potential beneficial and harmful effects of that particular drug and to know how specific clinical characteristics might modify the probability of a wanted outcome.

Fluoroquinolones are antibacterial agents that are increasingly used in primary care due to their broad spectrum, good oral absorption, and relatively few serious adverse reactions. However, since their introduction fluoroquinolones have been associated with reports of tendinitis. During the past years, the number of reports has risen, possibly because of the increased use of fluoroquinolones. Although many case reports on tendon disorders attributed to the use of fluoroquinolones have been published, there is still little quantitative information on the frequency and determinants of such disorders. This thesis presents several pharmaco-epidemiological studies in which the association between fluoroquinolone use and the occurrence of tendon disorders has been studied.

Chapter 1 gives a general introduction to this thesis. In **chapter 2**, the utilisation of fluoroquinolones in the Netherlands in the period 1991-1996 is described and compared to the utilisation of fluoroquinolones in several other western countries. In the Netherlands, a large increase in use of fluoroquinolones was observed in the community during the period 1991 through 1996. The total number of DDD per 1,000 inhabitants per day increased by 131% from 0.26 in 1991 to 0.57 in 1996. In this period, use of ofloxacin increased by more than 600 %; use of ciprofloxacin by 133 %, and use of norfloxacin by 76 %. For all age classes, there was an increase in use but in persons above 60 years of age the increase was highest. This rise in fluoroquinolone use is in line with the increased use in Canada, Germany, Italy, the UK, Spain, and the USA. On the contrary, there was a decrease in fluoroquinolone use in France and Australia after 1994. Large differences in the use of individual fluoroquinolones in the different countries were observed.

In **chapter 3**, we describe a series of 42 spontaneous reports of fluoroquinolone-associated tendon disorders which were reported to the Netherlands Pharmacovigilance Foundation Lareb and the Drug Safety Unit of the Inspectorate for Health Care between 1 January 1988 and 1 January 1998. The data concerned 32 (76 %) patients with a tendinitis and 10 (24 %) patients with a

tendon rupture. Sixteen (38 %) cases were attributed to ofloxacin, 13 (31 %) to ciprofloxacin, 8 (19 %) to norfloxacin and 5 (12 %) to pefloxacin. There was a male predominance and the median age of the patients was 68 years. Most of the reports concerned the Achilles tendon, and 24 (57 %) patients had bilateral tendinitis. The latency period between start of treatment and onset of symptoms was usually two weeks, but sometimes only a few days. Most patients recovered within 2 months after cessation of therapy, but a substantial part (26 %) had persistent symptoms. These reports suggest that fluoroquinolone-associated tendon disorders are more common in patients over 60 years of age. Ofloxacin was implicated most frequently relative to the number of filled prescriptions in the Netherlands.

The potential public health effects of an association between fluoroquinolone use and tendon ruptures in the Netherlands are addressed in **chapter 4**. The expected number of fluoroquinolone-attributable tendon ruptures was calculated on the basis of the use of fluoroquinolones, the number of non-traumatic tendon ruptures, and an assumed relative risk varying between 1.5 and 10. Data on fluoroquinolone use were obtained from the PHARMO database, and nation-wide hospitalisation data on tendon ruptures, from the Dutch Center for Health Care Information. The 'population' exposure prevalence was defined as the age and gender standardised number of fluoroquinolone episodes per 10,000 persons per month. The 'population' exposure prevalence of fluoroquinolones increased rapidly from 7 to 17 per 10,000 persons per month between 1991 and 1996. The absolute number of hospitalized non-traumatic tendon ruptures increased simultaneously from 768 to 984. This increase occurred mainly in patients over 60 years of age. Assuming a relative risk varying from 1.5 to 10.0, it appears that 1 to 15 tendon ruptures could be attributed to fluoroquinolone use in 1996. Only 7 % of the observed increase could be attributed to the increased use of fluoroquinolones.

The study described in **chapter 5** focused on the quantification of the association between fluoroquinolone use and tendinitis. We carried out a retrospective cohort study in a dynamic population to study the association between fluoroquinolone use and all forms of tendinitis. Data came from the IPCI-database which includes all data on consultations, morbidity, prescriptions and other interventions, as registered by GPs in a source population of approximately 385,000 persons. All persons treated with either fluoroquinolones, amoxicillin, trimethoprim, co-trimoxazole 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 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. Although we observed heterogeneity among the different fluoroquinolones, implying that the risk was highest for ofloxacin we had not enough power to prove this.

In **chapter 6**, we examined the association between fluoroquinolone use and Achilles tendon disorders in more detail using a larger sample. A nested case-control study was performed in a cohort of approximately 50,000 fluoroquinolone users in the IMS HEALTH United Kingdom Primary Care Database (UK *MediPlus*®). This system contains data on consultations, morbidity, prescriptions, and other interventions as registered by general practitioners in a source population of approximately 1-2 million inhabitants. The cohort included 46,776 persons aged 18 to 95, who had received at least one prescription of a fluoroquinolone in the period between July 1, 1992 and June 30, 1998. Potential cases were defined as a first time registration of Achilles tendinitis or Achilles tendon rupture. A group of 10,000 control patients were randomly sampled from the study cohort with a random date included in the follow-up period of that individual taken as index date. We identified 742 patients with Achilles tendon disorders of whom 704 had an Achilles tendinitis and 38 had an Achilles tendon rupture. The adjusted relative risk of Achilles tendon disorders following current use of fluoroquinolones was 1.9 (95%CI: 1.3-2.6). Among patients of 60 years and older the relative risk was 3.2 (95%CI: 2.1-4.9) as against 0.9 (95%CI: 0.5-1.6) among patients younger than 60. In the elderly, the relative risk was 11.5 (95%CI: 5.2-25.7) for current use of ofloxacin, while the relative risks were 2.3 (95%CI: 1.4-4.0) and 1.8 (95%CI: 0.4-8.0) for ciprofloxacin and norfloxacin. In patients of 60 years and older, concurrent use of corticosteroids and fluoroquinolones increased the risk to 6.2 (95%CI: 3.0-12.8).

In **chapter 7**, we present a population-based case-control study on the association between fluoroquinolone use and Achilles tendon rupture. Data came from the General Practitioners Research Database (GPRD), which contains computerised medical information on approximately 4 million inhabitants in the United Kingdom. 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 prior to 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.

We identified a total of 1367 cases that met the inclusion criteria. The adjusted relative risk of Achilles tendon rupture was 4.2 (95%CI: 2.3-7.6) for current exposure to fluoroquinolones. Age appeared to be a strong modifier of the effect. The relative risk of Achilles tendon rupture was 6.4 (95%CI: 3.0-13.7) in patients of 60-79 years, 20.4 (95%CI: 4.6-90.1) in patients 80 years of age, while among patients younger than 60 there were no currently exposed cases to fluoroquinolones. Concomitant use of oral corticosteroids increased the overall risk to 14.5 (95%CI: 5.9-36.6).

Finally, in **chapter 8** the results of our studies are discussed and comments on clinical relevance and suggestions for further research are given. Our studies in this thesis confirm that fluoroquinolones may cause Achilles tendinitis and Achilles tendon rupture, especially when combined with oral corticosteroids in elderly. The attributable risk may be substantial in the very old although also in this age-group the contribution of other factors to Achilles tendon rupture prevails. Although the risk is probably highest for ofloxacin, we were not able to find a statistically significant difference with the other fluoroquinolones in most studies.

SAMENVATTING

De keus om een bepaald antibacterieel middel voor te schijven zou in principe moeten afhangen van het antibacteriële spectrum en de evaluatie van de balans werkzaamheid/schadelijkheid voor elke patiënt. Dit vereist dat een voorschrijver de gunstige maar ook de schadelijke effecten van dat specifieke geneesmiddel moet kennen. Bovendien moet hij weten of, en zo ja hoe bepaalde klinische kenmerken de kans op een bepaalde uitkomst kunnen veranderen.

Fluorochinolonen zijn antibacteriële middelen die, vanwege hun brede spectrum, goede orale absorptie en relatief weinig ernstige bijwerkingen, in toenemende mate worden gebruikt in de eerste lijn. Sinds hun introductie echter, zijn er ziektegeschiedenissen gepubliceerd waarin peesontsteking als bijwerking van fluorochinolonen wordt beschreven. Het aantal gepubliceerde ziektegeschiedenissen is gedurende de laatste jaren toegenomen, mogelijk vanwege de stijging in gebruik van fluorochinolonen. Hoewel er inmiddels vele ziektegeschiedenissen zijn gepubliceerd over peesaandoeningen, toegeschreven aan het gebruik van fluorochinolonen, is er nog steeds weinig bekend over de frequentie en de determinanten van deze bijwerking. In dit proefschrift worden verschillende farmaco-epidemiologische studies gepresenteerd waarin de relatie tussen het gebruik van fluorochinolonen en het voorkomen van peesaandoeningen wordt bestudeerd.

Hoofdstuk 1 is een algemene inleiding tot dit proefschrift. In **hoofdstuk 2** wordt het gebruik van fluorochinolonen gedurende de periode 1991-1996 in Nederland beschreven en vergeleken met het gebruik van fluorochinolonen in verschillende andere westerse landen. In de periode 1991-1996 nam in Nederland het gebruik van fluorochinolonen enorm toe. Het totaal aantal DDD per 1000 inwoners per dag steeg met 131 % van 0,26 in 1991 tot 0,57 in 1996. In deze periode nam het gebruik van ofloxacin toe met 600%, het gebruik van ciprofloxacin met 133% en het gebruik van norfloxacin met 76%. De toename in het gebruik van fluorochinolonen werd in alle leeftijdscategorieën gezien maar was het grootst bij personen boven de 60 jaar. Deze stijging in het gebruik van fluorochinolonen is in overeenstemming met de toename in gebruik in Canada, Duitsland, Italië, Spanje, het Verenigd Koninkrijk en de Verenigde Staten van Amerika. Daar staat echter tegenover dat in Frankrijk en in Australië na 1994, het gebruik van fluorochinolonen afnam. Er werden grote verschillen in gebruik van de individuele fluorochinolonen in de verschillende landen geconstateerd.

In **hoofdstuk 3** beschrijven we een serie van 42 spontane meldingen van peesaandoeningen, die werden toegeschreven aan het gebruik van fluorochinolonen. Deze meldingen werden tussen 1 januari 1988 en 1 januari 1998 gemeld aan de Stichting Landelijke Registratie Evaluatie Bijwerkingen (Lareb) en de Sectie Geneesmiddelenbewaking van de Inspectie voor de Gezondheidszorg. Het betrof 32 (76 %) patiënten met een peesontsteking en 10 (24 %) patiënten met een peesruptuur. Zestien (38 %) ziektegeschiedenissen werden toegeschreven aan het gebruik van ofloxacin, 13 (31 %) aan ciprofloxacin, 8 (19 %) aan norfloxacin en 5 (12 %) aan pefloxacin. Het merendeel van de patiënten was man. De mediane leeftijd was 68 jaar. De meeste meldingen hadden betrekking op de Achillespees en bij 24 (57 %) patiënten was de tendinitis bilateraal. De latentieperiode tussen het begin van de behandeling en de aanvang van de symptomen was meestal 2 weken, maar soms ook enkele dagen. De meeste patiënten herstelden binnen 2 maanden na stopzetting van de behandeling met fluorochinolonen maar bij een substantieel gedeelte van de patiënten (26 %) persisteerden de symptomen. Deze meldingen suggereren dat peesaandoeningen door fluorochinolonen relatief vaakvoorkomen bij patiënten boven de 60 jaar. In relatie tot het aantal in Nederland afgeleverde prescripties kwam de bijwerking het meest voor bij ofloxacin.

De potentiële effecten van een associatie tussen het gebruik van fluorochinolonen en het ontstaan van peesrupturen voor de gezondheidszorg in Nederland worden beschreven in **hoofdstuk 4**. Op basis van het gebruik van fluorochinolonen, het aantal niet-traumatische peesrupturen en een verondersteld relatief risico tussen de 1,5 en 10 werd het verwachte aantal met gebruik van fluorochinolonen samenhangende peesrupturen berekend. Uit de PHARMO database werden gegevens over het gebruik van fluorochinolonen verkregen en van de Stichting PRISMANT de landelijke opnamegegevens betreffende peesrupturen. De 'populatie' expositie prevalentie werd gedefinieerd als het naar leeftijd en geslacht gestandaardiseerde aantal episodes fluorochinolonen per 10.000 personen per maand. De 'populatie' expositie prevalentie van fluorochinolonen steeg tussen 1991 en 1996 van 7 naar 17 episodes per 10.000 personen per maand. Het absolute aantal ziekenhuisopnames wegens niet-traumatische peesrupturen nam tegelijkertijd toe van 768 naar 984. Deze toename vond voornamelijk plaats bij patiënten boven de 60 jaar. Wanneer wordt verondersteld dat het relatieve risico tussen de 1,5 en 10,0 ligt, zouden in 1996 slechts 1 tot 15 peesrupturen toegeschreven kunnen worden aan het gebruik van

fluorochinolonen. Van de waargenomen stijging van peesrupturen kan slechts 7 % worden verklaard door de toename in het gebruik van fluorochinolonen.

In **hoofdstuk 5** ligt het accent op het kwantificeren van de associatie tussen het gebruik van fluorochinolonen en het optreden van een peesontsteking. Hierbij hebben we de IPCI-database gebruikt om een retrospectieve cohort-studie uit te voeren in een dynamische populatie. De IPCI-database bevat alle gegevens over consulten, morbiditeit, voorschriften en andere interventies, zoals die worden geregistreerd door huisartsen in een populatie van ongeveer 385.000 personen. Alle personen die werden behandeld met ofwel fluorochinolonen, amoxicilline, trimethoprim, co-trimoxazol of nitrofurantoine, werden vanaf de eerste dag van behandeling gevolgd tot het optreden van een peesontsteking, het veranderen van praktijk, overlijden of het einde van de studieperiode. De studiecohort bestond uit 1841 patiënten die fluorochinolonen gebruikten en 9406 patiënten die één van de andere antibacteriële middelen gebruikten. Het gecorrigeerde relatief risico op een peesontsteking bij fluorochinolon gebruikers was 3,7 (95% BI: 0,9-15,1) voor Achillespeesontsteking en 1,3 (95%BI: 0,4-4,7) voor andere vormen van peesontsteking. Hoewel wij verschillen tussen de relatieve risico's voor de individuele fluorochinolonen waarnamen, waren de verschillen niet statistisch significant.

In **hoofdstuk 6** hebben wij in een grotere steekproef de associatie tussen het gebruik van fluorochinolonen en het optreden van peesaandoeningen verder onderzocht. Hierbij maakten we gebruik van een patiënt-controle onderzoek, genest in een cohort van ongeveer 50.000 fluorochinolon gebruikers in de IMS HEALTH United Kingdom Primary Care Database (UK *Mediplus*®). Deze database bevat gegevens over consulten, morbiditeit, voorschriften en andere interventies, zoals die worden geregistreerd door huisartsen in een bronpopulatie van ongeveer 1 tot 2 miljoen inwoners. De studiecohort bestond uit 46.776 personen van 18 tot 95 jaar, die in de periode van 1 juli 1992 tot en met 30 juni 1998 minstens één prescriptie voor een fluorochinolon hadden ontvangen. Potentiële 'cases' werden gedefinieerd als een eerste registratie van Achillespeesontsteking of Achillespeesruptuur. Een groep van 10.000 controle-patiënten werden aselect getrokken uit de studiecohort met een aselect gekozen datum in de vervolgperiode van de persoon als indexdatum. Wij identificeerden 742 patiënten met een Achillespeesaandoening; 704 patiënten hadden een Achillespeesontsteking en 38 een Achillespeesruptuur. Het gecorrigeerde relatieve risico op een Achillespeesaandoening bij gebruik van fluorochinolonen

bedroeg 1,9 (95%BI: 1,3-2,6). Het relatieve risico bedroeg 3,2 (95%BI: 2,1-4,9) voor patiënten van 60 jaar en ouder, terwijl voor patiënten jonger dan 60 jaar het relatieve risico 0,9 (95%BI: 0,5-1,6) was. In de groep ouderen, bedroeg het relatieve risico 11,5 (95%BI: 5,2-25,7) bij huidig gebruik van ofloxacin, terwijl het relatieve risico voor ciprofloxin 2,3 (95%BI:1,4-4,0) bedroeg en voor norfloxacin 1,8 (95%BI:0,4-8,0). Bij patiënten van 60 jaar en ouder bleek, dat bij het tezamen gebruiken van corticosteroïden en fluorochinolonen het relatieve risico toenam tot 6,2 (95%BI: 3,0-12,8).

In **Hoofdstuk 7** presenteren wij een patiënt-controle onderzoek naar het verband tussen het gebruik van fluorochinolonen en het ontstaan van Achillespeesrupturen. De gegevens voor dit onderzoek waren afkomstig van de General Practice Research Database (GPRD). Deze database bevat over ongeveer 4 miljoen inwoners in het Verenigd Koninkrijk gecomputeriseerde medische informatie. We vergeleken alle personen die voor het eerst een Achillespeesruptuur hadden met een controlegroep van 50.000 aselect getrokken personen met 18 maanden historie. Aan deze controlepersonen werd een willekeurige datum als indexdatum toegekend. In totaal waren er 1367 patiënten, die aan de inclusie criteria voldeden. Het gecorrigeerde relatieve risico op een Achillespeesruptuur bij gebruik van fluorochinolonen was 4,2 (95%BI: 2,3-7,6). Leeftijd bleek het effect sterk te beïnvloeden. Het relatieve risico op een Achillespeesruptuur was 6,4 (95%BI: 3,0-13,7) bij patiënten van 60 tot 80 jaar en 20,4 (95BI: 4.6-90.1) bij patiënten van 80 jaar en ouder. Het gelijktijdig gebruiken van orale corticosteroïden verhoogde het relatieve risico tot 14,5 (95%BI: 5,9-36,6).

In **Hoofdstuk 8** ten slotte worden de belangrijkste bevindingen van onze studies bediscussieerd en worden suggesties voor verder onderzoek gegeven. Onze studies in dit proefschrift bevestigen dat fluorochinolonen Achillespeesontsteking en Achillespeesruptuur kunnen veroorzaken, vooral wanneer ze met orale corticosteroïden worden gecombineerd bij ouderen. Het attributieve risico kan bij de zeer ouderen substantieel zijn, hoewel ook in deze leeftijdsgroep de bijdrage van andere risicofactoren voor Achillespeesruptuur belangrijk blijft. Hoewel het risico waarschijnlijk het grootste is voor ofloxacin waren wij in de meeste studies niet in staat om een statistisch significant verschil met de andere fluorochinolonen aan te tonen.

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CURRICULUM VITAE

Paul Diederik van der Linden was born on November 17th, 1966 on Curaçao, the Netherlands Antilles. He graduated in 1987 at the "Johan van Oldenbarneveld Gymnasium" in Amersfoort, the Netherlands (secondary school; "Gymnasium ß"). In that same year he started his pharmacy study at the Utrecht University, in Utrecht, the Netherlands. During this period he performed a research project at the Department of Pharmacoepidemiology & Pharmacotherapy (Dr. E. van Ganse), Utrecht Institute for Pharmaceutical Sciences, on asthma, antiallergic and antitussive medication in relation with asthma exacerbations. He obtained his pharmacist's degree in 1995 after which he worked as a research associate at the Department of Medical Informatics (head: Prof.dr.ir. J.H. van Bemmel), Erasmus Medical Center Rotterdam. In 1996 he started his research project, described in this thesis at the Department of Epidemiology & Biostatistics (head: Prof.dr. A. Hofman), Erasmus Medical Center Rotterdam, in close collaboration with the Department of Pharmacoepidemiology & Pharmacotherapy (head: Prof.dr. H.G.M. Leufkens), Utrecht Institute for Pharmaceutical Sciences. In 1998, he obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. As of November 1999, he started his training as a hospital pharmacist at the Department of Clinical Pharmacy of the Reinier de Graaf hospital in Delft.