Fluoroquinolone use and the change in incidence of tendon ruptures in the Netherlands

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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 more often fluoroquinolones 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.

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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. The most frequently observed adverse effects are of gastro-intestinal origin, followed by CNS disorders and skin reactions [2-4].

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 [5,6] and in 1991 the first case of Achilles tendon rupture in a fluoroquinolone-treated patient was published [7]. 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 [5,8-14]. 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 [15]. 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 [11,13,16].

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 [17]. 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 [18]. 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 [19], 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 1 months-population exposure prevalence of fluoroquinolone use and RR as the relative risk of tendon rupture associated with exposure to fluoroquinolones [20]. So, if a person used 1 prescription of a fluoroquinolone in one year, he or she was considered as exposed for one month while the other 11 months contributed to non-exposure person-time. 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 [18]. 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 more often fluoroquinolones 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 in patients of 60 years and older in 1996.

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,

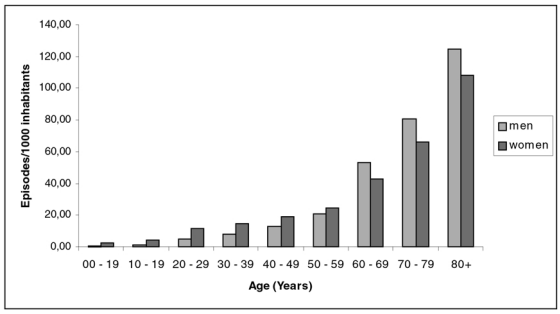
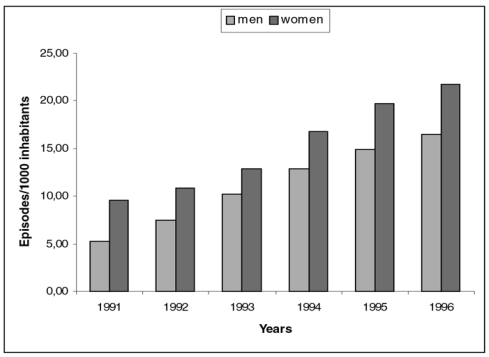


Figure 1.
Incidence of fluoroquinolone use in 1996 by age and gender

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	87	86	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



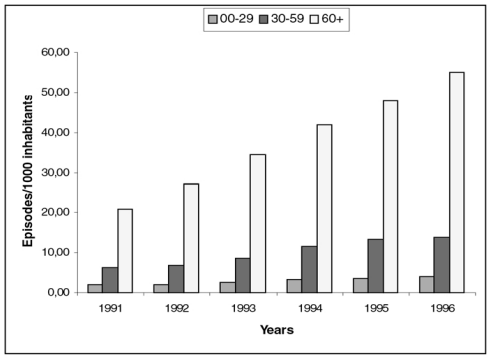
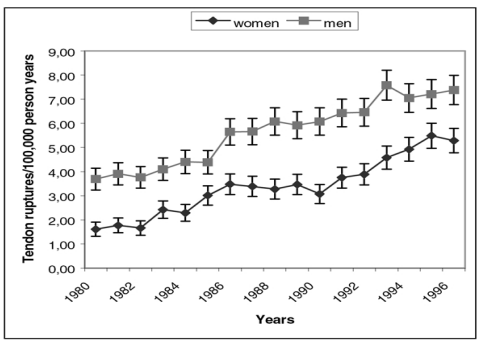


Figure 2a & b.
Incidence of fluoroquinolone use in the period 1991-1996 stratified for gender and age



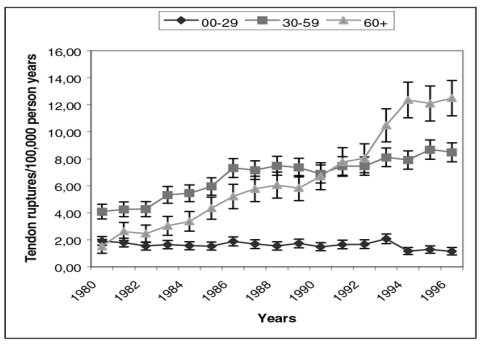


Figure 3a & b.
Incidence of non-traumatic tendon ruptures in the period 1980-1996, stratified by gender and age

0.09 to 1.51 % of the admitted patients with non-traumatic tendon ruptures in the Netherlands were 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.

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 15 cases per year can be attributed to the use of fluoroquinolones.

In the Netherlands, a large increase in 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 [21], but in the Nordic countries [22] 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 in women may be explained by relatively frequent treatment of urinary tract infections with norfloxacin. The increased use in 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

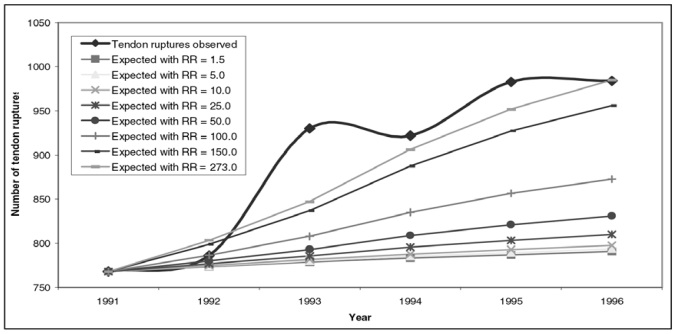


Figure 4.

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

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 [23]. Therefore, our figures are probably an adequate estimation of use in the community but an underestimation of 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 use of fluoroquinolones would be 20 per 10 million inhabitants, which is still low. This number may increase in the future due the recent introduced fluoroquinolones levofloxacin, grepafloxacin and sparfloxacin, and the subsequently rising trend in fluoroquinolone use. Another potential source of misclassification comes from our risk window of 30 days which is compatible with the observation that 90% of the published case-reports occur within 30 days after first intake. Would we assume a risk window of 60 days for every prescription, the population attributable risk percentage would double to 3%.

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.

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.

Acknowledgement

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