06-6974

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Joan Claybrook, President

August 29, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing more than 100,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately add a black box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics presently on the market in the United States [Ciprofloxacin (Cipro; Bayer), Enoxacin (Penetrex; Aventis), Gatifloxacin (Tequin; Bristol-Myers Squibb), Levofloxacin (Levaquin; Ortho-McNeil), Lomefloxacin (Maxaquin; Unimed), Moxifloxacin (Avelox; Bayer), Norfloxacin (Noroxin; Merck), Ofloxacin (Floxin; Daiichi-Sankyo)]. We also urge the FDA to mandate a "Dear Doctor" letter to warn physicians of these adverse effects and require the distribution of an FDA-approved Medication Guide for all patients, to be dispensed when the prescriptions are filled. From November 1997 through December 31, 2005, the FDA had received reports of 262 cases of tendon rupture in patients using one of the above-listed fluoroquinolone antibiotics.

Public Citizen supports the Office of the Illinois Attorney General in their previous petition to add a black box warning to fluoroquinolones regarding this serious adverse event. Dr. Arnold Widen, Medical Director of the Illinois Attorney General's Office and Dr. Babs Waldman, Medical Director of the Health Care Bureau of the Attorney General's Office filed the petition on May 28, 2005, but have not received a substantive response from the agency.

Public Citizen has a ten year history of concern about fluoroquinolone-induced tendinitis and tendon rupture.

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We successfully petitioned the FDA on August 6, 1996 to place a warning regarding the risk of tendinitis and tendon rupture on the package inserts of all fluoroquinolones. Although, at the time, we thought this would effectively educate physicians and patients about this adverse event, a simple non-bolded warning buried in the list of possible adverse reactions to fluoroquinolones has been grossly inadequate. Fluoroquinolone-induced tendon ruptures continue to occur at an alarming rate (175 reports of rupture since the beginning of 2003) and there is thus an urgent need for a black box warning regarding the risk of tendinitis and tendon rupture.

Public Citizen's concern is based, in part, on our analysis of the FDA adverse event database in patients receiving fluoroquinolones. That analysis shows 1) 262 cases of tendon ruptures; 2) 258 cases of tendinitis; and 3) 274 cases of other tendon disorders (see Table 1).

Methodology

We searched the FDA Adverse Event database (November 1997 to December 31, 2005) for all adverse reaction reports in which the primary suspect drug was one of the fluoroquinolones presently on the market in the United States. We used the terms "tendon rupture," "tendon disorder," "tendon disorder NOS," tendon injury," "tendonitis," "tendonitis exacerbated (the preferred dictionary spelling is tendinitis but the FDA database uses tendonitis)," "rotator cuff syndrome," and "rotator cuff." We limited the search to initial (not follow-up) reports. It should be noted that reports of tendon rupture and other tendon pathology prior to November 1997 are not included in our analysis since they are in another FDA database. We also limited this search to initial reports to avoid counting duplicate reports.

The entire FDA Adverse Event database for all drugs was also searched for "tendon rupture" to determine the drugs most commonly associated with this event. .

Results

The FDA estimates that only about ten percent of all adverse events are actually reported to the adverse event database and therefore the number of tendon ruptures is likely approximately ten times these numbers.

Table 1. Types of Tendon Pathology

Type of Tendon Pathology	Totals
Tendon Rupture	262
Tendinitis	258
Tendon Disorder (other)	274
Total	794

Although 61 percent of fluoroquinolone-associated tendon ruptures were associated with levofloxacin, (see Table 2 below), this drug has been the most heavily prescribed fluoroquinolone over the past four years, accounting for approximately 45 percent of all fluoroquinolone prescriptions during that time.

Table 2. Tendon Ruptures for each fluoroquinolone

Drug	N	Percentage
Levofloxacin	159	61%
Ciprofloxacin	60	23%
Moxifloxacin	23	8.8%
Gatifloxacin	11	4.2%
Ofloxacin	7	2.7%
Norfloxacin	1	0.3%
Lomefloxacin	1	0.3%
Total	**262**	**100%**

An analysis of the entire FDA Adverse Event database revealed that fluoroquinolones were implicated significantly more often in tendon ruptures than any other class of drugs (38 percent of all tendon ruptures were thought due to fluoroquinolones). The mean age of patients with tendinopathy was 58.9 years for the cases in the database. Three hundred and twenty four males and 318 females experienced tendinopathy (gender was reported in only 642 cases).

While performing the analysis, we discovered a curious association between statins and tendon ruptures. Statin-induced tendinopathy has been reported as case reports in the literature.[1] However, fluoroquinolones were approximately 5 times more likely to be associated with tendon rupture than statins after adjusting for the much larger number of prescriptions written

for statins than fluoroquinolones over this given time period. Nevertheless, the association between statins and tendinopathy warrants further evaluation.

Table 3. Tendon Ruptures by Drug Class

Drug	N	Percentage
Fluoroquinolones	262	38.1%
Statins	168	24.5%
Corticosteroids	27	4.0%
Other (drugs <15 cases)	230	33.5%
Total	**687**	**100%**

BACKGROUND

Achilles tendon rupture causes sudden severe pain; difficulty walking; and swelling and bruise formation in the affected area prompting immediate medical attention. The treatment is either surgery or casting for 6 to 8 weeks followed by months of physical rehabilitation. Tendonitis causes pain and swelling in the affected tendon and is treated by removing the offending agent, anti-inflammatory medication, rest, and physical rehabilitation.

A recent review of the literature regarding fluoroquinolone-associated tendinopathy found 98 cases, 88 (89.8 percent) of which involved the Achilles tendon.[ii] There were 40 cases of tendon rupture in these 98 patients. The mean age in this review was 59 years, which was the same as the mean age of 59 years in the FDA Adverse Event database. The ratio of men to women in this review was 1.9:1 and the ratio was 1.02:1 in the FDA database.

Achilles tendon rupture has classically been a sports-related injury with an average age of 35 years in the general population. Two-thirds of achilles tendon ruptures occur in men.[iii] The demographics of tendon rupture are vastly different in people who recently took fluoroquinolones compared to the demographics of tendon rupture in the general population. This finding suggests a strong causative link between fluoroquinolone use and tendon rupture. The mean age in the FDA adverse event database as well as in the literature-reported quinolone-associated cases is nearly twenty-five years older than the mean age of Achilles tendon rupture in the general population. The predilection toward males in those Achilles tendon ruptures occurring in the general population was not seen in the FDA adverse event database as evidenced by the nearly equal distribution of cases between genders. It is hypothesized that men, usually younger men, in the general

population participate in more high-impact activities that increase their risk of Achilles tendon rupture. The older age and female predominance of quinolone-associated tendon injury presumably reflect patterns of drug use.

Although the exact mechanism of injury in fluoroquinolone-associated tendinopathy is unknown, it is widely speculated that fluoroquinolones are directly toxic to tendon fibers possibly associated with further decreased blood supply that particularly targets tendons that generally have a limited blood supply to begin with.[iv] Achilles tendon ruptures normally occur 2 to 6 cm above the calcaneus (heel bone), which correlates with the area of the tendon with the poorest blood supply[2]. There have also been reported cases of tendinopathies occuring after a single dose suggesting a direct toxic effect.[v] Patients with poor renal function also have a higher risk of fluoroquinolone-associated tendinopathy. This is likely due to increased toxicity of the drugs due to decreased renal clearance[3].

THE CURRENT LABEL

The FDA issued a statement in the October 1996 issue of its Medical Bulletin to all manufacturers of fluoroquinolones requesting a revision of the package inserts to include a new paragraph in the "Warnings" section acknowledging the risk of tendonitis and tendon rupture in fluoroquinolones. The warning is among a list of other potential side effects and is in plain, non-bold type. While the wording of the warning is accurate, it is inappropriately buried in a long list of potential adverse reactions. Physicians need to be educated about this risk as evidenced by the markedly increased number of reported tendon ruptures since 1998 as seen in Table 3. This could either be due to an increase in physician reporting of this adverse reaction or increased number of prescriptions written. No matter the cause, fluoroquinolone-induced tendon ruptures persist (and may be increasing) despite the re-labeling of the package insert in 1996 with a buried warning. Fluoroquinolone-induced tendon rupture is quite characteristic of this class of drug and we feel this serious reaction warrants a more pronounced black box warning that will better alert physicians and patients of this complication.

Table 3. Number of reported tendon ruptures in the FDA Adverse Event database per year: 1998-2005

Year	Reported tendon ruptures
1998	5
1999	0
2000	19
2001	26
2002	37
2003	65
2004	47
2005	63
Total	**262**

The content for our model "Black Box" warning would be:

Fluoroquinolone antibiotics should be used with extreme caution because there is an increased risk of tendinitis and the possibility of complete tendon rupture with all fluoroquinolone antibiotics.

This adverse reaction most frequently involves the Achilles tendon, the tendon that runs from the back of the heel to the calf. Rupture of the Achilles tendon may require surgical repair. Tendons in the rotator cuff (the shoulder), the hand, the biceps, and the thumb have also been involved. This reaction appears to be more common in those taking steroid drugs, in older patients, and in kidney transplant recipients, but many cases have occurred in people without any of these risk factors. The onset of symptoms is sudden and has occurred as soon as 24 hours after starting treatment with a fluoroquinolone.

If you experience pain in any tendon while taking these medications you should stop the medication and immediately contact your physician so you can be switched to another antibiotic.

ENVIRONMENTAL IMPACT STATEMENT

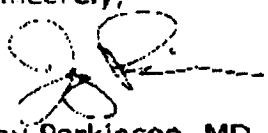
Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

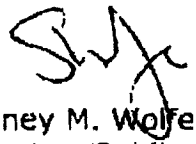
We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it

includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,



Jay Parkinson, MD, MPH
Research Analyst



Sidney M. Wolfe, MD
Director, Public Citizen's Health Research Group

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[i] Chazerain, P. Four Cases of Tendinopathy in Patients on Statin Therapy. Joint Bone Spine 2001 ; 68 : 430-3.

[ii] Khaliq. Y. Fluoroquinolone-Associated Tendinopathy: A Critical Review of the Literature. Clinical Infectious Diseases 2003; 36:1404–10.

[iii] Ufberg. J. Orthopedic Pitfalls in the ED: Achilles Tendon Rupture. American Journal of Emergency Medicine 2004; 22: 596-600.

[iv] Le Huec. J. Epicondylitis after treatment with fluoroquinolone antibiotics. J Bone Joint Surg Br 1995; 77:293–5.

[v] Van der Linden, P. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. BMJ 2002; 324: 1306-07.