CHAPTER 3

FLUOROQUINOLONE TOXICITY TO TENDONS, JOINTS, MUSCLES AND BONES

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Despite the many reports of tendon, joint, and muscle injuries with FQs during the 1980s, Cipro was approved in the U.S. in 1988 with inadequate warnings of the harm the drug could do. By the early 1990s, the flow of injury reports intensified. For example, a 1992 report described a case of bilateral Achilles tendon ruptures in a person on an FQ. Achilles tendon ruptures are unusual unless from trauma (football, running, climbing, car accident). Bilateral Achilles tendon ruptures are even rarer. In this case there was no trauma. The cause had to be something else.

In 1994, a report from France described 100 cases of tendon injuries including 31 tendon ruptures with FQs. Also in 1994, Dr. K. Huston published a letter in the New England Journal of Medicine describing an eighty-five-year-old man, already on prednisone (a steroid) for a rheumatologic disorder, who developed rupture of his right Achilles tendon following treatment with an FQ. Worried by what occurred, Dr. Huston added prophetically,

Fluoroquinolone antibiotics have been associated with Achilles tendinitis and rupture in reports from Europe and New Zealand. This unusual side effect has not been widely recognized in the United States and is not mentioned in the Physicians’ Desk Reference. Physicians should be aware of this potential complication.
We might wonder why, with so many reports, health care professionals in the United States were not made quickly aware of the problem. Unfortunately Huston’s statement, even in one of our very top medical journals, made little impact. By 1997, the *Physicians' Desk Reference* (PDR) did mention tendinitis in its description of Cipro, but you’d have to look hard to find it. The PDR information on Cipro occupied three entire pages of the voluminous book. Among 900 lines of information, the warning about tendon reactions comprised a barely visible five lines mentioning that inflammation, muscle pain, tendinitis, or tendon rupture could occur with Cipro. Most doctors probably never noticed it.

**Reports of FQ Injuries Keep Coming**

From the fourth quarter of 1997 to the fourth quarter of 2012, the FDA received 12,088 reports of individual cases of FQ-related injuries to people’s musculoskeletal systems. As explained in Chapter 2, these cases included only those in which FQs were listed as the primary precipitant, that is, the highly probable cause of the injury. Tendon rupture occurred in 2,141 of these 12,088 FQ cases. Imagine, more than 2,000 people suffering tendon ruptures, muscle being ripped from bone, and often other injuries as well. Who could have imagined an antibiotic could do such damage? A tendon rupture means extreme pain, prolonged incapacity, surgery, and in many cases, disability and, because these injuries do not always heal completely, an uncertain future.

As explained in Chapter 2, these FDA cases may represent only 1–5 percent of the actual cases that have occurred. Do the math: it equates to at least 242,000 cases of musculoskeletal injury and 40,000 cases of tendon rupture over a period of fifteen years. These numbers are hard to fathom, and a more accurate study should have been undertaken.

**Onset of Musculoskeletal Injuries**

In a 2011 study conducted at the Mayo Clinic, doctors found that “Fluoroquinolone associated tendinopathy symptoms have occurred as early as 2 hours after the initial fluoroquinolone exposure and as late as 6 months after the medication was discontinued.”

Could a serious reaction to an FQ occur within hours after the first pill? Yes. I once served as an expert witness in a case of a woman with myasthenia gravis (a disease that weakens muscles) who received Cipro. Her husband was suing the doctor. The woman died within two
hours of taking her first Cipro pill. They had waited at the doctor’s office for fifteen minutes after she took Cipro just to be safe, then they went shopping. As the medication took full effect, it weakened the woman’s already compromised respiratory muscles, and she died of asphyxiation before the paramedics could arrive. Even though the Cipro package insert lists myasthenia gravis as a contraindication for using FQs, the doctor had no idea such harm could result. Reading the medical records, I felt this was a good doctor. If he was unfamiliar with the clear warnings about the serious risks of FQs for his patient, how many other doctors are unfamiliar with this and other contraindications to using FQs?

**TABLE 3.1 FDA Medication Guide for Fluoroquinolone Antibiotics**

Patients are supposed to receive this information with a FQ prescription, but many don’t. The guides are written by FQ manufacturers and approved by the FDA. The FDA recommends getting immediate medical help if any of the following adverse effects occur:

Tendon rupture or swelling of the tendon (tendinitis): Tendon problems can happen in people of all ages who take FQs. Tendons are tough cords of tissue that connect muscles to bones. Symptoms of tendon problems may include pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or any other tendon site.

The risk of getting tendon problems while you take an FQ is higher if you are over sixty years of age; are taking steroids (corticosteroids); have had a kidney, heart, or lung transplant or kidney failure. Other factors include physical activity or exercise, previous tendon problems, or disorders that can involve tendon problems such as rheumatoid arthritis.

Tendon problems can happen in people who do not have the above risk factors when they take FQs. In other words, they can occur in young and healthy people too.

Tendon ruptures have happened up to several months after patients have finished taking their FQs.

Get medical help right away if you get any of the following signs or symptoms of a tendon rupture: hearing or feeling a snap or pop in a tendon area; inability to move the affected area or bear weight; or bruising right after an injury in a tendon area.
FQs can interfere with the muscles controlling breathing in people with myasthenia gravis (a disease that causes muscle weakness). In this population, tendon injuries can cause difficulty breathing, respiratory distress, or death.

**Severity of Tendon Injuries**

Tendons are fibrous tissues, made primarily of protein-rich collagen, that connect muscles to bones. Tendons convey the power of muscle contractions onto bony structures, thereby moving the bones. For example, to bend your elbow, your biceps muscle contract, the biceps tendon carries the contraction to the elbow, and your forearm bends toward your shoulder.

Healthy tendons are essential for normal voluntary movement of the body. Tendon inflammation or injury can cause pain at rest and especially with use. Although Achilles rupture is the most notorious and recognized adverse drug event of FQs, any tendon in the body is vulnerable. Injuries to tendons of the hand, elbow, shoulder, foot, ankle, knee, thigh, and eye muscles have been reported in medical journals. I have spoken to many people whose injuries involved multiple tendons. When the injury is severe and involves more than one tendon, disability often occurs. People cannot move without pain, so they restrict their motion. One man spent his first year after FQ toxicity on his couch, going into the kitchen or bathroom only when necessary.

FQ injuries can affect other body systems too: central nervous system, peripheral nervous system, cardiovascular or gastrointestinal systems, skin, and so on. One man recently reported widespread tendon pain accompanied by high anxiety, insomnia, dizziness, weakness, nerve pain in his legs, and intense heart palpitations.

FQ reactions impacting tendons may be brief (days or weeks), or they may last a few months, or many months or years. In 1997–2012, among the FDA’s 12,088 cases of FQ-induced musculoskeletal injury were disabilities that occurred in 2,138 cases. As time went on and some of these people did not heal, my guess is that the number of disability cases grew.

**Frequency of Tendon Injuries and Ruptures**

Different studies have projected different numbers, but one reliable source is the journal *Drug Safety*, which concluded,
Evidence that exposure to fluoroquinolones is associated with the sudden occurrence of tendinitis is supported by this large population based study. We can estimate that a single case of rupture of the Achilles tendon would occur for every 5958 persons treated with fluoroquinolones.8

This means about 165 cases per million people treated with fluoroquinolones. Since the FDA estimates that over 23 million outpatient prescriptions were filled for FQs in 2011 in the United States, that’s 3,795 cases of Achilles ruptures that year.

Other studies have estimated that around two cases of tendon injuries occur per 10,000 people taking an FQ. And with tendon ruptures at about 1 per 10,000, this translates to about 4,600 tendon injuries and 2,300 tendon ruptures in 2011. These numbers are consistent and therefore credible.

The numbers increase if we consider the unknown yet substantial numbers of inpatient prescriptions for FQs given in U.S. hospitals. People over sixty have a higher risk of FQ reactions, and people in hospitals are often over sixty. And remember, cases reported to the FDA represent only 1–5 percent of actual incidents, so we need to multiply the above numbers by a factor of as much as twenty or more.

Table 3.2 Proven and Suspected Risk Factors for FQ-Related Musculoskeletal Injuries

Proven Risk Factors

- Concomitant use of corticosteroids
- Age sixty or older
- Sports activities or intense exercise
- Magnesium deficiency
- Trauma to tendons or joints
- History of organ transplantation
- End-stage kidney disease and/or hemodialysis

Additional Suspected Risk Factors

- Osteoarthritis or rheumatoid arthritis
- Systemic lupus erythematosus
- Ankylosing spondylitis
Reiter’s syndrome
Polymyalgia rheumatica
Ulcerative colitis
Crohn’s disease
Diabetes mellitus
Hypothyroidism
Hyperparathyroidism

Impact on Tendons

FQs can cause injury in a single tendon or in many at one time. The main symptom is pain. The tendon injuries caused by FQs resemble overuse injuries in athletes, similar to repetitive stress injuries. Technically, tendons injured by FQs develop abnormal tendon fiber structure, areas of abnormal fibrous tissue, thickening of tendons, and swelling. Studies of FQs in dogs demonstrate reductions in normal collagen and elastin in tendon tissue and reduced production of new collagen, all of which are necessary for healing. Premature cell death (apoptosis) also occurs, which explains the prolonged weakness and slow pace or lack of healing seen in tendon injuries caused by FQs.

Impact on Cartilage and Bone

The FDA acknowledged in its upgraded warnings on FQs in 2008 that “Fluoroquinolones exert a toxic effect not only on tendons but also on cartilage, bone and muscle.”

The FDA always chooses its words carefully because of the medico-legal implications of its statements. Several studies have identified the toxic effects of FQs on cartilage. Cartilage lesions display swelling of cartilage matrix, reduced cartilage cell growth and cell metabolism, increased inflammation, and oxidative damage.

The Mayo Clinic has shown that FQs can slow bone healing. Because of this, they recommend avoidance of FQs in patients with fractures or recovering from joint replacement surgery unless FQs are the only effective antibiotic for an infection.
Impact on Joints

The PDR states that joint pain occurs in approximately 1 percent of patients taking FQs. Other studies have reported substantially higher rates. A frequent complaint of people with FQ reactions is a clicking or grating sound from one or multiple joints with movement. These sounds may occur with or without pain. It is thought that the sounds are the result of swelling or inflammation within the joint, causing audible noise when swollen or inflamed tissues move against one another or against bone.

Impact on Muscles

Muscle pain (myalgia) is a common complaint with FQs. The myalgia may range from mild muscle pain that fades within a few weeks after discontinuing the FQ to severe myopathies and even a rare, life-threatening muscle breakdown syndrome known as rhabdomyolysis. If this is suspected, a blood test, creatine phosphokinase (CK or CPK), should be done as soon as possible.

Age and Gender Factors

When the FDA states that people age sixty or older are most vulnerable to FQ musculoskeletal injury, some health care professionals think this means FQs are not a risk for younger people. This isn’t correct.

In many studies, the average age of people developing FQ-related tendon injuries is fifty to fifty-five, meaning that more than half of them were younger than the stated at-risk age of sixty or older. In our analysis of FDA data, only 39 percent of the FDA cases involved people sixty or older. So overall, these injuries occur more often in younger people than older. This is important information for doctors and consumers to know. In terms of sheer numbers, many people in their teens, twenties, thirties, forties, and fifties get floxed too. For this reason, FQs should be used judiciously with every age group.
FQ Use in Children

FQs should not be prescribed for children and adolescents unless absolutely necessary. The FDA makes exceptions only for serious infections that are not sensitive to or have not responded to other antibiotics. Despite these restrictions on FQ use in children, 520,000 prescriptions for FQs were filled in 2002 in the United States for those younger than eighteen years.23

There are reasons why FQs are restricted in children. In studies of FQs used in young rats and beagle dogs, FQs caused extensive damage to their developing cartilage.24 In 2006, the Committee on Infectious Diseases of the American Academy of Pediatrics recommended the following:

Fluoroquinolone use should be restricted to situations in which there is no safe and effective alternative to treat an infection caused by multi-drug resistant bacteria or to provide oral therapy when parenteral [intravenous] therapy is not feasible and no other effective oral agent is available.25

This restriction should apply not only to children, but to everyone. Nevertheless, there has been some debate in the medical literature about whether the evidence supports restricting FQ use in youngsters. Two studies have found no evidence that FQs cause a greater frequency of musculoskeletal disorders than other antibiotics.26-27 Yet, in a study that compared adverse events in several thousand children given Levaquin in comparison to adverse events with other non-FQ antibiotics, there was a greater incidence of musculoskeletal problems with Levaquin. These adverse effects included joint pain, arthritis, tendon pain, or impaired walking. Other studies have also shown that FQs produce a higher frequency of musculoskeletal problems in children than other antibiotics.28-30

My view is that the restrictions on FQs in children are correct. In addition, the FDA warning about FQ use in children should be extended to everyone. FQs should not be used as first choice drugs for any condition unless other antibiotics are ineffective or laboratory testing shows that the bacteria are sensitive only to FQs. In other words, my rule for FQ use should be: USE ONLY WHEN NECESSARY!
Pregnancy

For the same reasons that FQs are generally contraindicated in children, they are contraindicated in pregnant women. FQs should be used with utmost caution in women of childbearing age, especially those who are attempting to become pregnant. FQs also should be used with caution in women who are sexually active, especially those not consistently using birth control.

FDA Actions

Finally in 2008, twenty-one years after the approval of Cipro, the FDA required stronger warnings in the information on FQs in the PDR and in the package inserts available at pharmacies. The black-box warning, framed by thick black lines, stated, “Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture in all ages.” Farther down, the warning describes the ravages caused by FQs during animal research:

In immature rats and dogs, the oral and intravenous administration of FQs resulted in increased osteochondrosis [cartilage damage]. Histopathological examination of the weight bearing joints of immature dogs dosed with fluoroquinolones revealed persistent lesions of the cartilage.

Clearly, the injuries to tendons, muscles, joints, and bones from FQs were apparent early from animal studies and also in the early use of FQs in people in other countries. Many of the problems we’ve been seeing for nearly thirty years in the United States certainly could have been avoided or at least minimized. So, too, could many of the other toxicities that FQs can cause people.

The drug safety system in this country is nonexistent. It is a disgrace. I will discuss this in much greater depth in the final chapter of this book.
NOTE TO READERS:

SUBSEQUENT CHAPTERS WILL BE MADE AVAILABLE TO THE PUBLIC EVERY 7-10 DAYS UNTIL LATE OCTOBER, WHEN THE FULL BOOK WITH ALL 16 CHAPTERS WILL BE PUBLISHED IN LATE OCTOBER AND AVAILABLE BY SOFTBACK AND BY E-BOOK.

UPCOMING CHAPTERS HERE WILL INCLUDE:

4. Fluoroquinolone Toxicities to the Central and Peripheral Nervous Systems

5. Fluoroquinolone Toxicity Syndrome in Other Areas of the Body
   - C. Diff Acute Pseudomembranous Colitis
   - Cardiac Arrhythmias
   - Psychiatric Disorders
   - Post-Traumatic Stress Disorder
   - Sunlight Photosensitivity Syndrome

6. Doctors, the FDA, and Fluoroquinolone Toxicity Syndrome

7. Do Fluoroquinolones Damage Human DNA?

AT THIS POINT, THE BOOK WILL BE RELEASED IN COMPLETE FORM WITH ITS LARGE SECTION TWO: EVIDENCE-BASED TREATMENT POSSIBILITIES AND OTHER CONSIDERATIONS FOR PREVENTING FLUOROQUINOLONE TOXICITY SYNDROME AND HELPING THOSE ALREADY INJURED. THIS SECTION OF THE BOOK WILL CONTAIN 8 CHAPTERS WITH IDEAS FROM EVIDENCE-BASED MEDICINE AS WELL AS MANY UNIQUE IDEAS FROM MEDICAL AND ALTERNATIVE APPROACHES.

THE BOOK IS EXPECTED TO MEASURE 200 PAGES
CHAPTER 3 REFERENCES

Fluoroquinolone Toxicity to Tendons, Joints, Muscles, and Bones


