Fluoroquinolone Toxicity

Oliver Newell, a member of the senior staff of the Lincoln Laboratory of the Massachusetts Institute of Technology, took his own life on September 21, 2012 after struggling for seven months with a syndrome of severe antibiotic side effects. The condition Oliver had is best described as fluoroquinolone (FQ) poisoning. He was prescribed the FQ drug Cipro in February of this year to deal with a suspected urinary tract or prostate infection. This condition appears to be caused by a broad attack by the drug on many of the body's systems. Although many people with this condition do improve substantially after months to years of suffering, some do not survive it, and there are plenty who are left with permanent effects.

About half of the FQ drugs have been taken off the market due to serious side effects, including Tequin, Omniflox, Trovan, and Zagam. Those that remain include Levaquin, Cipro, Avelox, Floxin, and others.

The drugs are powerful agents that act by disrupting the action of enzymes that manipulate bacterial DNA. The original quinolone drugs without fluorine could have serious side effects. Fluorine was added to the drug to help it to penetrate tissues so that it could fight infections in parts of the body, particularly connective tissues like the urinary tract and bladder, that older antibiotics could not easily reach. So the drug was designed to have low free energy barriers for entry into body tissues. Unfortunately, this means that the drug is also more likely to interact with these tissues than older drugs. The fluorine substituent seems to give the drug a passport into many body systems. For those who are susceptible, it can damage many of these systems. It's possible that the systems of everyone who takes it are affected to some extent, since the effects seem to be cumulative, with some of those who experience serious side effects reporting that they had taken the drug before without noticing problems. It's also important to note that it is not only orally administered FQs that cause problems. Serious side effects have been reported even when the drug is taken externally in the form of drops.

This table, taken from the webpage http://www.medicationsense.com/fluoroquinolone.html that is referenced below, is a summary of typical effects experienced by sufferers of this condition:

Peripheral Nervous System: Tingling, numbness, prickling, burning pain, pins/needles sensation, electrical or shooting pain, skin crawling, sensation, hyperesthesia, hypoesthesia, allodynia (sensitivity to touch), numbness, weakness, twitching, tremors, spasms.
Central Nervous System: Dizziness, malaise, weakness, impaired coordination, nightmares, insomnia, headaches, agitation, anxiety, panic attacks, disorientation, impaired concentration or memory, confusion, depersonalization, hallucinations, psychoses.
Musculoskeletal: Muscle pain, weakness, soreness; joint swelling, pain; tendon pain, ruptures.
Special Senses: Diminished or altered visual, olfactory, auditory functioning, tinnitus (ringing in the ears).
Cardiovascular: Tachycardia, shortness of breath, hypertension, palpitations, chest pain.
Skin: Rash, swelling, hair loss, sweating, intolerance to heat and\or cold.
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain.

When we showed Oliver this table, he told us that he had experienced or was experiencing most or all of these effects. He had severe muscle weakness, and would complain that after using his muscles a few times they would become exhausted. He also had tendon pain and joint pain and swelling. He had peripheral nervous system problems like burning sensations and tingling. He had skin problems like frequent rashes, and his skin seemed to

be more easily damaged. He had gastrointestinal problems, vision issues, ringing in the ears, insomnia, and palpitations. I don't think Oliver could tell us the extent of the problems he had with the central nervous system. We knew about his anxiety and panic attacks, and were alarmed by them because before taking the drug Oliver was a rock.

A number of these symptoms are listed on the Cipro label. But the label does not make clear that taking even a single Cipro pill can lead to a very broad, disabling and long-lasting syndrome of effects. The label also warns of suicidal thoughts, and suicides do happen amongst those who have taken these drugs.

The mechanism(s) by which FQ drugs damage tissues are not well understood. Unfortunately, the FQ drugs may have a greater tendency to interact with the cellular structures of non-bacterial organisms like us than older drugs like tetracycline, erythromycin, and penicillin. Penicillin, for example, attacks bacterial cell walls, which is a mechanism with relatively low risk for us because our cells have no cell walls, just cell membranes. FQ drugs act against bacteria by disrupting the action of enzymes that manipulate bacterial DNA. But they may also affect the DNA-manipulating enzymes in our cells. FQ drugs may be capable of damaging our chromosomes. For reasons that are not understood, the drugs are highly toxic to mammalian cells in culture. Tendon tissues of affected individuals examined well after exposure to the drug have shown damage similar to overuse injuries in athletes. FQs may directly attack the structure of connective tissues, which would be consistent with their often rapid effects. They may attack the chondrocyte cells that maintain the tissues. The drug shows strong synergistic effects with corticosteroids, which themselves are known to weaken connective tissues. According to one study, tendon ruptures are 46 times more likely to occur in those taking corticosteroids together with FQs than in those taking FQs alone. FQ toxicity may be related to interactions between the drug and important receptor complexes in the body. For example, a blockade by Cipro of the receptor complexes for GABA, which is the main inhibitory neurotransmitter in the central nervous system, could lead to continuous excitation of nerves which may cause overuse damage and damage from oxidative stress. FQ toxicity may be related to effects on the mitochondria, which are the organelles that are the "power plants" of our cells. Mitochondria may have evolved from captured bacteria, and may therefore be vulnerable to attack by FQs as bacteria are. Loss of energy due to mitochondrial toxicity may be consistent with the extreme muscle fatigue of the FQ syndrome – Oliver told us time and again that he could use his muscles just 3 or 4 times before they would become fatigued.

Although reports of musculoskelatal problems with the quinolones had been coming in since 1972, the FDA resisted taking action for decades. Finally, in 2008, they were forced by lawsuits from the group Public Citizen to include a black box warning on FQs indicating increased risk of tendon ruptures. This is the most serious kind of warning the FDA can issue and still keep the drug on the market. It has been estimated that 2 to 6 percent of achilles tendon ruptures in those greater than 60 years old are caused by FQ drugs. The FDA added a second black box warning to Cipro in 2011 concerning its potential to worsen the symptoms of myasethenia gravis, including muscle weakness. Some generic versions of the drug may still not carry these warnings, however.

The side effects of FQ drugs often do not stop after a person stops taking them. In fact, the effects may not become obvious until after a person has finished the drug. A possible explanation for this is that the tissues are weakened by the drug, and ordinary use then becomes overuse. Damage from this overuse may then accumulate over time until symptoms become obvious, and tissues can fail. This process of overuse injury can continue over many months to years, and throughout the process, new symptoms can appear as the damage to each system becomes large enough to be noticeable. Recovery is then a battle between the healing powers of the body and the tendency of weakened tissues to fail with use. Another possible explanation for the long-lasting effects is that chromosome damage disrupts the ability of cells to produce new protein components.

There is almost no help available from the medical community for those suffering from FQ poisoning. Many doctors don't understand the issue and refuse to acknowledge that the drug is the cause. You go from one doctor to another, from GPs to rheumatologists to infectious disease doctors to neurologists, but there is no help or treatment. Doctors are frustrated and must have difficulty admitting to themselves that they damaged a patient in

this way, and there also may be concerns about lawsuits. As in Oliver's case, doctors will even prescribe steroids to reduce inflammation, apparently unaware that this can make the condition worse because of the huge synergy between Cipro and steroids.

Why doesn't everyone experience this syndrome? Although at the tissue level, the body systems perform the same functions in everyone, genetic differences lead to differences in body structures at the molecular level that do not effect tissue function in a major way in healthy people, but mean that some people can be more susceptible than others to particular drugs. It's also true that many people who have taken FQs without noticeable symptoms once can end up being disabled after taking it again at a later time. This suggests that the effects can be cumulative, and it's very important to realize that a person is not safe taking these drugs again just because they have taken them before and not noticed problems. With Oliver, we thought that perhaps interactions between multiple antibiotics may have contributed to his condition, since he took doxycycline and Bactrim just before Cipro. But many get this condition without taking any other drugs.

Why is this syndrome not more widely reported? Delayed effects are one likely reason - since symptoms may not appear for weeks or months after a person has stopped taking the drug, the patient and doctor can miss the connection between the drug and the symptoms. Another major reason is that most doctors are only aware of the tendon effects. When patients go to them with this awful syndrome, they often respond that Cipro can't possibly be the cause. And this is self-perpetuating. Since doctors don't believe FQs are responsible, they don't issue accurate adverse event reports, so other doctors are not made aware of the problems. There is also an inherent conflict of interest in the event reporting system, because the doctor that prescribed the drug is supposed to report that they took an action which disabled their patient. So we can't know the actual incidence of serious side effects with these drugs. In addition, even the FDA agrees that its system for reporting side effects, the Adverse Event Reporting System, is outdated and inadequate, and catches only about 10% of side effects. Even so, the system report 2500 deaths linked to (though not necessarily caused by) quinolones and another 45,000 negative side effects between 1997 and 2010. Judging by the number of reports available on the web from non-FDA sources, it's likely that at least ten thousand people have experienced this syndrome. It may be that ten thousand or more people get the syndrome every year. According to the website lawyersandsettlements.com, Johnson and Johnson faces tens of thousands of lawsuits from users of the FQ drug Levaquin who allege that the drug caused tendon injury, irreversible nerve damage, and other serious side effects. It has been suggested that heavy use of FQs among women to treat UTI's is connected to the incidence of chronic fatigue syndrome and fibromyalgia, which are two conditions that also involve weakness and tendon problems.

We are not saying that these drugs should never be used. But drugs that can have such disabling, untreatable long-term side effects should only be prescribed as a last resort to treat the most serious conditions when other, safer drugs will not do the job, and patients should be informed of the risks of getting the syndrome. The problem is that these drugs are routinely prescribed for conditions like sinus infections that may not even have a bacterial component, and they are often prescribed before the results of bacterial cultures are received. Since millions of prescriptions are written each year, very large numbers of people are being unnecessarily exposed to the risks of these drugs. In 2010, Levaquin was the best-selling antibiotic on the market.

There are a number of web sources with information about FQ reactions, although some have apparently been forced to shut down by Bayer, the manufacturer of Cipro. A good summary page, which has the table of symptoms we've included in this document, is:

http://www.medicationsense.com/fluoroquinolone.html

There is a PBS Newshour video from last year (2011) at:
http://www.pbs.org/newshour/bb/health/jan-june11/antibiotics_06-16.html

This a NYT health piece from September 10 2012 on the issue, which Oliver forwarded to us:
http://well.blogs.nytimes.com/2012/09/10/popular-antibiotics-may-carry-serious-side-effects/?ref=health

This web page, put together by the sufferer who wrote the first testimonial below, lists 21 important points about FQs and the response of the medical community to them:
www.ciproispoison.com

This is the website of the Quinolone Vigilance Foundation, an organization formed to understand quinolone toxicity and reduce its incidence:
www.saferpills.org

Some peer-reviewed research has been done on separate side effects of FQs, particularly on its effects on tendons. This is a review of tendon research:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921747

This is a study from JAMA this year on how FQs lead to an almost fivefold higher risk of retinal detachments:
http://jama.jamanetwork.com/article.aspx?articleid=1148331

This August 2012 abstract from PubMed describes a mini-review of research done on the effects of antimicrobials, including FQs, on mitochondria:
http://www.ncbi.nlm.nih.gov/pubmed/22615289

As far as we know, however, very little work has been done on the debilitating syndrome of effects that FQs can cause.

The best database of patient reports that we know of is at www.askapatient.com. The pages at this site for Cipro, Levaquin and Avelox make devastating reading. There are about two thousand of reports of serious, often disabling side effects, including reports from MDs who were themselves affected. Many of these reports contain detailed descriptions of syndromes of effects, and many of these exactly match Oliver's experience. Many contain email contact addresses. New reports are constantly being added. As of 10/03/2012, the most recent report for Cipro is from 4 days previous, 9/30/2012. The Cipro page at askapatient.com is at:

http://www.askapatient.com/viewrating.asp?drug=19537&name=CIPRO (or just go to www.askapatient.com and enter “Cipro” in the search box).

Here are three reports from the askapatient.com Cipro page written by people with the syndrome:

Posted 3/8/2012:

Destroyed my entire life in so many ways I cannot even begin to tell you. Bedridden for the past 2.5 years with no end in sight. I was 30 years old and healthy prior to ingesting just TWELVE of these poison pills. No one EVER warned me they could permanently cripple me! Had I even half a clue of what this poison is capable of I wouldn't have come within 100 feet of it!!! I went from beyond healthy (minus some bladder pain) to now having more health problems than I could possibly list here, many of them disabling and disfiguring in and of themselves. Every hour of every day I must fight off the urge to end once and for all this horrific existence that is now my "life". I really don't know how much longer I can hold out. Doctors know NOTHING about this medication or it's devastating consequences, and Bayer--those f'ing criminals--are of absolutely NO help once they've got your money and you've fallen victim to their poison!

Posted 4/8/2012 by a physician:

Fluoroquinolones can cause a severe reaction that hasn't been fully appreciated by the medical community. I am a physician and I know how ignorant we are with regards to the side effects. The FDA warning doesn't take a strong stand against the side effects and fails to mention that Fluoroquinolones lead to a SYNDROME with many side effects. To believe this class of medications causes one or another side effect is completely irresponsible of the FDA. As a physician and as someone that is suffering the Fluoroquinlone syndrome/toxicity, I beg the FDA to limit the use of Fluoroquinolones to life and death situations, and to recognize that Fluoroquinolones can lead to a syndrome that can last months if not years. If it wasn't for my vacation and sick leave days, and the kindness and understanding of my empoyer, I would be out of a job! Yes, a Physician at age 43 out of a job and on disability. This is proposterous to say the least. The FDA must take the sufferes seriously. Prior to this toxicity, I was a healthy, physically active person. I had NO medical history. For God's sake, I had never taken any meds except a few motrins and Tylenols here and there. This medication has completely made my life miserable. I feel like a 300 year person. Please, I beg the FDA to take a moral and ethical stand above monetary gains, and limit the use of these meds, and to better inform the public of the syndrome that may arise, and believe me, as a sufferer, the symptoms aren't your garden variety symptoms. THEY ARE FROM HELL!

Posted 8/24/2012:

43 year old athletic male, soccer player since high school, and avid weight lifter. Felt like superman. I developed UTI symptoms and decided to take a safe medication. I had taken CIPRO 8 years ago and didn't recall any side effects. This time around took the antibiotic and went to Hell. I have experienced side effects that have damaged every organ...joint pains, stomach pains, cartilage destruction, neuropathic pains (burning skin, pin and needles, and so forth), and on and on, worst side effects were depression that made me suicidal, anxiety that was from Hell, severe insomnia, eye pains, ringing in the ears, loss of short term memory, brain fog, unable to focus eyes, and tons more. The medical community is ignorant of the syndrome that Fluoroquinolones cause. Trust me if you haven't suffered this syndrome yet, you WILL if you continue taking it. The good news is after 7 1/2 months I have noticed some improvements. Avoid this family of antibiotics like the plague. If you haven't experienced any of its side effects, consider being given a second, a third, forth chance, but if you continue taking it especially the 500 mg and above tablets you WILL suffer. The 250 mg tablets may be below the toxic range and most people can tolerate them well, but the 500 mg tables will get you eventually!

Please consider this information before taking an FQ drug yourself or allowing a loved one to take one, and spread the word about this to everyone you know. Please send the link to this document to your email contacts. If we had received this information earlier, Oliver may not have ever taken the drug. This is a public health emergency. If you have any influence in the worlds of medicine, biological research, or law that could make a difference, please use it. Doctors need to be immediately educated about this disabling syndrome. More research needs to be done on the effects of these drugs. The FDA needs to put in place a much more effective system for reporting adverse events. Reports should be mandatory for every prescription issued, and should include the patient’s reports of their symptoms. And the system should track patients well after they have taken a drug, so that delayed reactions can be reported.

Best wishes and thank you for coming,

The Newell family