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The perils of prescribing fluoroquinolones

These broad-spectrum antibiotics—notable for combatting pathogens resistant to other drugs—have a small but noteworthy potential for adverse effects. This review and patient handout highlight signs and symptoms to watch for.

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PRACTICE RECOMMENDATIONS

› *Evaluate liver function before initiating fluoroquinolone (FQ) therapy, and avoid prescribing these antibiotics for patients at increased risk for hepatotoxicity.* (C)

› *Avoid prescribing FQs for patients with a history of prolonged QT syndrome.* (C)

› *Closely monitor older patients being treated with FQs, particularly if they have atherosclerosis or epilepsy.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Sara Z, a 62-year-old patient with a history of chronic urinary tract infections, presents with a 3-day history of dysuria and urinary frequency. Her last 2 urine cultures found *Escherichia coli* resistant to trimethoprim-sulfamethoxazole, amoxicillin, and cephalosporins. So her family physician ordered a urine culture and prescribed a 7-day course of ciprofloxacin empirically.

Five days later, Ms. Z returned, suffering from nonbloody diarrhea and bilateral Achilles tendon pain.

If you were treating Ms. Z, what would your next step be?

Widely used to treat urinary tract, skin, and pulmonary infections and to fight infections resistant to other antibiotics, fluoroquinolones (FQ) are generally regarded as safe in both inpatient and outpatient settings. Yet these broad-spectrum antibiotics are associated with both common and rare adverse effects, as well as a number of drug-drug interactions.

The Centers for Disease Control and Prevention estimates that adverse events from FQs leading to emergency department (ED) visits occur at a rate of 9.2 for every 10,000 prescriptions. That's higher than the ED rates for cephalosporins (6.1 per 10,000) and macrolides (5.1 per 10,000), but far lower than for penicillins (13 per 10,000), clindamycin (18.5 per 10,000), sulfonamides (18.9 per 10,000), and vancomycin (24.1 per 10,000).[1]

In fact, adverse events associated with FQs range from mild and self-limiting to rare and severe. This review discusses both. Relatively common adverse effects and drug-drug interactions are discussed in the text, while the **TABLE**[2] includes a broader range of potential adverse effects. You'll also find a handout for patients taking FQs on page 195 that clearly describes signs and symptoms that need to be reported right away.

CONTINUED

Adverse effects of fluoroquinolones result in ED visits at an estimated rate of 9.2 per 10,000 prescriptions.

A black box warning of tendinopathies

FQs exhibit an affinity for connective tissue, with higher concentrations found in bone and cartilage than in serum. While FQs are therefore well suited for treating orthopedic-related infections,[3] they also increase the risk of tendinopathies.

In the last 2 decades, numerous case reports linking tendinitis and FQs have been published.[4-6] In 2008, the US Food and Drug Administration (FDA) issued a black box warning of tendinitis and tendon rupture. Patients on FQ therapy should be advised to stop taking the antibiotic at the first sign of pain, swelling, or inflammation in a tendon, the FDA advises.[7]

How common is this adverse effect? A case-control study of 22,194 patients with a diagnosis of nontraumatic tendinopathy determined that FQ use resulted in a 1.3-fold risk of tendon rupture and more than a 4-fold risk of rupture of the Achilles tendon. One Achilles tendon rupture would occur for every 5958 patients treated with FQs, the researchers estimated.[8]

The precise mechanism by which FQs lead to tendinopathies is not completely understood. Studies suggest that the antibiotics cause a decrease in the synthesis of type I collagen, elastin, fibronectin, and beta (1)-integrin, and time- and concentration-dependent increases of cellular apoptosis.[9] In vitro studies have shown inhibition of both cell proliferation and fibroblast metabolism when tissue is exposed to FQs, which may impede tissue healing.[10]

Which patients are at higher risk? The risk of FQ-associated tendinopathies is greatest in patients older than 60 years; in kidney, heart, and lung transplant recipients; and in patients taking an FQ with concomitant corticosteroid therapy. Decreased renal clearance of the medication may play a role in the increased risk.[11]

GI problems are common, especially in kids and older patients

Gastrointestinal (GI) disturbances are common in patients taking FQs, and typically occur more frequently in children and older adults, and in those taking higher doses. Reactions attributable to ciprofloxacin, for example, include nausea (affecting 1.4%-4% of adults and 2.7% of children taking the drug), vomiting (1%-2% of adults and 4.8% of children), diarrhea (<1%-2% of adults and 4.8% of children), and abdominal pain or discomfort (<1%-1.7% of adults and 3.3% of children).[12]

***C difficile* and FQ resistance.** The extent to which *Clostridium difficile*-associated diarrhea (CDAD) is attributable to FQs has been subject to controversy in recent years. A previously uncommon strain of *C difficile* (B1/NAP1) with variations that have become more resistant to FQs has been linked to an increased incidence of CDAD across both the United States and Europe.[13] A systematic review suggested that FQs predispose patients to CDAD,[14] while a retrospective case-control study of 174 adult inpatients with CDAD determined that FQ administration did not significantly increase the rate of complications from *C difficile* (odds ratio [OR]=1.37; 95% confidence interval [CI], 0.72-2.61).[15]

Factors that affect risk of hepatotoxicity

Hepatitis/transaminitis, pancreatitis, jaundice, liver injury, and hepatic failure have all been reported in patients taking FQs, with the extent of hepatotoxicity varying based on the particular FQ taken, the dosage, and the patient's baseline hepatic function.[16,17] Comorbidities, including renal failure, may increase the potential for FQ-associated hepatotoxicity, as well. Thus, some experts recommend that clinicians evaluate a patient's liver function before initiating FQ therapy and avoid prescribing FQs for those at added risk.

The exact mechanism by which FQ-induced hepatotoxicity occurs is unknown. One theory posits that the drugs generate oxidative radicals involved in mitochondrial damage, RNA processing, transcription, and inflammation;[18] another suggests that FQs generate oxidative radicals in the liver as a result of cytochrome P450 metabolism.[16] Case reports have shown that hepatitis resolves when the drug is discontinued, but often recurs in patients who are switched to a different FQ.[16,17]

TABLE

Fluoroquinolones: Adverse effects to guard against*[2]

Cardiovascular
- Hypotension
- Torsades de pointes

Dermatologic
- Eruption (angioedema, pruritus, rash, urticaria)

Drug-drug interactions
- Antacids (calcium carbonate, histamine-2 receptor antagonists)
- Antiarrhythmics
- Digoxin
- Ferrous sulfate
- Phenytoin
- Sucralfate
- Theophylline
- Warfarin†

Endocrine/Metabolic
- Glycosuria
- Hyper- and hypoglycemia

Gastrointestinal
- Diarrhea
- Hepatotoxicity
- Nausea/Vomiting

Hematologic
- Anemia
- Leukopenia
- Thrombocytopenia

Immunologic
- Anaphylactoid reaction
- Hypersensitivity reaction

Musculoskeletal
- Arthralgias
- Myalgias
- Polyarthritis
- Tendinopathies

Neurologic
- Confusion
- Dizziness
- Drowsiness
- Hallucinations
- Headaches
- Seizures

Ocular
- Diplopia
- Halos/hazy vision
- Photophobia
- Visual hallucinations

Psychiatric
- Psychoses
- Suicidal ideation

Respiratory
- Dyspnea

*This is not a complete list of potential adverse effects associated with fluoroquinolones.

†Fluoroquinolones may potentiate warfarin.

Older age and concomitant corticosteroid therapy are associated with a higher risk for fluoroquinolone-associated tendinopathy.

Torsades de pointes is the key cardiovascular risk

FQs prolong the QT interval by blocking voltage-gated potassium channels, causing a reduction of the rapid component of the delayed rectifier potassium current in a dose-dependent fashion.[19] But the average QT interval prolongation caused by FQs over a 3- to 6-month period does not appear to have clinical significance, nor is it associated with any discernible cardiac symptoms or impairment.[19]

For most, risk is minimal. There appears to be considerable variation in QT interval prolongation among FQs. A retrospective database analysis of published case reports of patients who received FQs over a 15-year period found 25 cases of torsades de pointes; moxifloxacin (highest), levofloxacin, and gatifloxacin (which was taken off the market by the FDA in 2006)[20] were associated with a higher incidence than ciprofloxacin.[21] Ciprofloxacin appears to be the safest FQ for cardiovascular events, with the lowest reported risk of torsades de pointes.[22] However, several small randomized controlled trials have found that levofloxacin, like ciprofloxacin, did not significantly affect the QT interval.[23,24]

These patients face a higher risk. Notably, individuals with abnormal baseline QT prolongation (>440 ms in men; >460 ms

in women) are at increased risk of developing torsades de pointes from the use of FQs, regardless of the dose.[19] In fact, anyone with a history of prolonged QT syndrome should avoid these antibiotics, particularly if he or she is taking class Ia (eg, procainamide, quinidine) or class III (eg, amiodarone, sotalol) antiarrhythmics.[19] Patients taking warfarin may be candidates for FQ therapy, but because the antibiotics may potentiate the anticoagulant, close monitoring is required. (Other potential drug-drug interactions are detailed in the **TABLE**.)

Evaluation of risk vs benefit is imperative prior to prescribing FQs for patients with increased risk for adverse cardiovascular events. An electrocardiogram is advisable, as well.

***Clostridium difficile* is increasingly resistant to fluoroquinolones, resulting in a higher incidence of *C difficile*-associated diarrhea in the United States and Europe.**

Mild neurologic and psychiatric effects not uncommon

Studies examining central nervous system (CNS) effects have estimated that neurotoxicity occurs in approximately 1% to 4.4% of patients taking FQs, with serious adverse effects occurring less than 0.5% of the time.[25] Common—and milder—CNS effects include headache, dizziness, and insomnia. More severe CNS effects include tremors, restlessness, anxiety, light-headedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and suicidal thoughts or attempts.[25,26] Case reports have documented FQ-induced psychosis, catatonia, seizures, and delirium, with a higher incidence associated with higher doses of the antibiotic.[26]

A literature review aimed at identifying case reports yielded reports of 232 adverse psychiatric and neurologic drug reactions attributable to FQs in 145 patients.[27] Nearly half were related to ciprofloxacin, with psychiatric reactions such as mania and acute psychosis being the most common. Most adverse CNS events (eg, convulsion, confusional state, agitation) developed rather quickly—in some cases within a few minutes of FQ administration and in others, within the first one to 8 days. In most reported cases, the patients had no known underlying psychiatric diseases or concomitant medication likely to have precipitated the development of delirium, psychosis, or seizures.[28]

Monitor older adults taking FQs. Because the risk of psychiatric adverse events is greatest in older individuals, especially those with known atherosclerotic disease or epilepsy, FQ therapy should be used cautiously—and with close monitoring—in this patient population. Symptoms such as weakness, confusion, tremor, loss of appetite, and depression are often incorrectly attributed simply to age, and thus go unreported as potential adverse effects of FQs.[29] The exact mechanism by which FQs may induce seizures is unknown, but it may be related to excitatory effects at GABA receptors in the hippocampus.[30]

FQs may affect glucose levels

FQs have been reported to have varying effects on glucose metabolism, and have been implicated in both hypo- and hyperglycemia. FQ-related hypoglycemia has been thought to occur as a result of an increase in insulin secretion through a sulfonylurea-like action on pancreatic beta cells,[31] via drug-drug interactions in patients with renal impairment,[32] or via cytochrome P450 interactions.[33] The mechanism of action relating to hyperglycemia is less well understood.

One retrospective cohort study in outpatients at a Veterans Administration facility sought to identify outcomes of hospitalization with a primary diagnosis of either hypo- or hyperglycemia in patients with a new prescription for either an FQ or azithromycin.[34] In patients with diabetes, the OR for FQ-associated hypoglycemia (compared with azithromycin) was 2.1 for levofloxacin (95% CI, 1.4-3.3) and 1.1 for ciprofloxacin (95% CI, 0.6-2.0). The ORs for hyperglycemia were 1.8 for levofloxacin (95%, CI 1.2-2.7) and 1.0 for ciprofloxacin (95% CI, 0.6-1.8).

A retrospective chart review of more than 17,000 hospitalized patients who were receiving either an FQ or ceftriaxone revealed that 101 patients had either high (>200 mg/dL) or low (<50 mg/dL) glucose levels within 72 hours of receiving the antibiotic.[35] Nearly 89% of those studied had diabetes and 40% had prescriptions for oral hypoglycemic agents. While most of these patients had

Taking a fluoroquinolone antibiotic?

Watch for these side effects

The antibiotic your doctor has prescribed is one of a group of medicines known as fluoroquinolones, or FQs for short. Like other antibiotics, FQs can destroy certain bacteria, but they do not work for illnesses that are caused by viruses, like the flu or the common cold.

This particular antibiotic usually kills the kind of bacteria that are making you sick, even though these "bugs" are stronger than (resistant to) many other common antibiotics. But like any medicine, it can cause a number of side effects. Most are mild, and will disappear when you finish taking the pills. But some are very serious—and, in rare cases, can lead to death. So it is important for you to pay close attention to the way you're feeling and to report anything unusual while you're taking this drug.

Call our office immediately (or have a family member or friend call) and stop taking this medicine if you have any of these possible side effects:

- seizures, hallucinations, depression, a noticeable change in your heartbeat (called an arrhythmia), or diarrhea.
- pain, swelling, inflammation, or a snap or pop in a tendon (the strong, fibrous tissue that connects muscles to bones)—especially the Achilles tendon, which is located at the back of the foot and connects the heel to the calf muscles.
- bruising right after an injury in a tendon area or the inability to walk normally.

Have you told your doctor…?

Your doctor should have a complete record of all your medical conditions and every medicine you take, including drugs or supplements that you buy without a prescription. If you remember something important that you forgot to tell the doctor, call our office and let us know.

underlying renal insufficiency, rates of hyperglycemia were greater with levofloxacin than with ceftriaxone. (In this study and the VA study, gatifloxacin had greater effects on glucose levels than the non-FQ antibiotics they were compared with; as noted earlier, however, gatifloxacin was removed from the US market in 2006.)

Diplopia is the most common ophthalmologic effect

A database review found 171 case reports of diplopia associated with FQs; ciprofloxacin was the most commonly implicated FQ, with 75 cases. The median time between medication initiation and the development of diplopia was 9.6 days. Most FQ-associated diplopia is completely reversible upon cessation of drug therapy, as evidenced by 53 published reports in which that was the case.[36]

Adverse effects of intraocular FQs. Ocular keratitis, corneal infiltrates and precipitates, and delayed corneal epithelial healing have been linked to the administration of intraocular FQs.[36-38] In addition, retinal detachment has been found to occur in 3.3% of patients being treated with intraocular FQs, compared with 0.6% of controls (adjusted rate ratio=4.50; number needed to harm= 2500).[39]

CASE ▶ Suspecting CDAD and Achilles tendinitis secondary to ciprofloxacin, you stop the medication. Ms. Z's urine culture is positive for *Klebsiella pneumoniae,* which is also sensitive to nitrofurantoin, so a 7-day course is prescribed. And, because a stool test for *C difficile* is positive, you prescribe a 7-day course of metronidazole, as well. Within 4 weeks of stopping the ciprofloxacin, the Achilles tendinitis had completely resolved. JFP

Headache, dizziness, and insomnia are common CNS effects, but fluoroquinolone-induced psychosis, catatonia, seizures, and delirium have also been reported in patients taking higher doses.

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