InFocus

Adverse Reactions to Fluoroquinolones

Part 2 in a Series

By James R. Roberts, MD

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All faculty and staff in a position to control the content of this CME activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

Learning Objectives: After reading this article, the physician should be able to:

1. Discuss the association of fluoroquinolone antibiotics and adverse CNS effects.
2. Explain the relationship of fluoroquinolones to seizures and their incidence in different types of patients.
3. Describe fluoroquinolone antibiotics' link to *Clostridium difficile* diarrhea.

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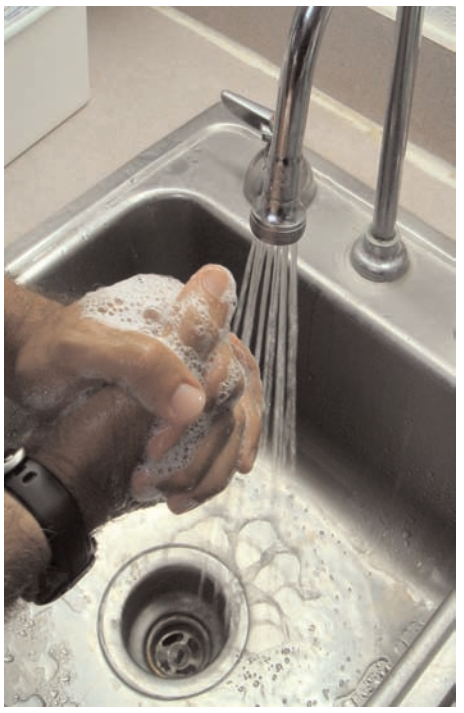

C. difficile **is the causative organism of antibiotic-associated colitis. It colonizes two percent of healthy adults who spread spores that live for weeks in the hospital. Harboring the organism or ingestion of spores predisposes patients to diarrhea when broad-spectrum antibiotics are prescribed, and normal GI flora is disrupted. Resistant** ***C. difficile*** **bacteria proliferate and generate toxins, and those toxins bind to intestinal epithelial cells, causing intense inflammation. Prevention of** ***C. difficile*** **diarrhea is twofold. The first approach is aimed at avoiding new colonization. Usually spores are spread by health care workers. Limiting diarrhea in already colonized patients is facilitated by eschewing antibiotics, such as quinolones, clindamycin, and cephalosporins. The ubiquitous alcohol-based hand disinfectants do not kill** ***C. difficile*** **spores, but vigorous hand washing with soap and water will. A new more virulent strain of** ***C. difficile*** **has emerged, and is correlated with quinolone use.**

Emergency physicians prescribe antibiotics on a daily basis, and except for concerns about allergies and selecting the right antibiotic for the right infection, little thought is given to other potential adverse effects. Although we occasionally see antibiotic-related side effects in the ED, such as drug-induced diarrhea, skin rashes, and GI upset, these adverse events are usually easily handled by simply stopping the antibiotic or choosing a different one. It's important to be cognizant of additional antibiotic-related adverse effects that may not be expected, and to recognize those that do not even make common sense to the intuitive mind.

Last month's column began a series of discussions on important, and universally underappreciated, adverse drug reactions to fluoroquinolone antibiotics that are relevant to the emergency physician. I noted some rather bizarre and totally unexpected complications to this class of antibiotics that has gained wide popularity. Many drugs of this class are prescribed with relative impunity, but a second cogitation is in order. While the majority of fluoroquinolones are well tolerated and have been proven to be excellent antimicrobials, some of the adverse reactions should be viewed as essential knowledge for emergency physicians. I am sure we have all seen most of them, but failing to relate the nonintuitive ones is likely quite common for us mere mortals.

I discussed the nuances of tendinopathy, from minor pain and dysfunction to overt tendon rupture associated with fluoroquinolones. Often the antibiotic has long been stopped, the patient has forgotten its use, or the doctor didn't ask about antibiotic use when the Achilles tendon ruptured. This month's column will focus on select CNS and GI side effects of fluoroquinolones.

Seizures Associated with Fluoroquinolones

Kushner JM, et al
Ann Pharmacother
2001;35(10):1194

This short article consists of two case reports and a review of current knowledge of quinolone-induced seizures. The ubiquity of quinolone use is highlighted, with the observation that these drugs are frequently used to treat various infections, including UTI, respiratory track infections, STDs, GI infections, and many skin and soft tissue infections. A number of CNS side effects have been noted with all quinolones, including headaches, dizziness, insomnia, tremors, confusion, psychosis, and grand mal seizures. The theoretical cause of CNS stimulation/dysfunction is binding of the antibiotic to GABA receptors in the brain. GABA blockade inhibits the natural endogenous neuro-inhibition properties of GABA, potentially rendering the patient prone to CNS excitability. True epileptic activity from quinolones is a rare event, but one that has been previously recognized.

Quinolones are generally considered to have the potential to lower the seizure threshold. The drugs are suggested to be used with caution in patients with a history of seizures or for those who are taking concomitant medications that also lower the seizure threshold. (I'm not sure how you use any drug with caution; you either use them or don't.) Quinolone-related CNS side effects can occur in otherwise normal patients and those with normal renal function. This report is not the first one relating overt generalized seizures to quinolone use. In fact, a similar concern has been in the package insert for some time. These cases are, however, the first levofloxacin-induced seizures without concomitant interacting therapy or mitigating circumstances. They occurred in patients with no history of a prior seizure disorder or a bona fide reason to have a convulsion. Neither patient had another obvious cause for the neurologic event.

The first case is that of a 75-year-old woman admitted for ischemic toes. She had a variety of concomitant diseases, including hypothyroidism, hypertension, CHF, and COPD. She was on a number of medications for these chronic conditions. The patient was prescribed oral levofloxacin (500 mg followed by 250 mg per day) while awaiting surgery. On the third day of levofloxacin therapy, the patient experienced a generalized tonic-clonic seizure. An LP and CT of the head were negative. No other cause for the seizure was found, and it did not recur following cessation of the quinolone therapy.

The patient experienced a variety of complications from her underlying diseases, and a month later, was rechallenged with ciprofloxacin (400 mg IV every 12 hours). Within one day, she experienced another generalized motor seizure. On discontinuation of ciprofloxacin, the patient remained seizure-free. Minor changes in renal function and sodium/magnesium levels were found, as have been previously reported with quinolone-related seizures, but likely these abnormalities by themselves would not cause a seizure.

In the second case, a 74-year-old woman was treated for bacterial pneumonia with levofloxacin (500 mg daily). After five doses, she experienced a generalized tonic seizure for the first time. No other cause for the seizure was found, and an LP and CT of the head were normal. This was an isolated seizure, and it was attributed to the antibiotic. This patient had normal electrolytes and renal function.

The authors provide a bibliography of 10 articles describing seizures with ciprofloxacin, ofloxacin, norfloxacin, and levofloxacin. Seizures occurred with standard doses, with both the oral and IV forms. Advanced age and higher quinolone serum levels secondary to renal failure may have been predispositions to quinolone-related seizures, but the data are unclear. Other specific predisposing factors for seizures would be electrolyte disturbance, such as low magnesium or sodium, hypocalcemia, hypoglycemia, or alkalosis. In patients with multiple medical problems, it is difficult to separate out one potential seizure-inducing parameter from another or to pinpoint the exact interaction of multiple variables. But in these cases, it seemed relatively clear that quinolones were at least partly culpable.

Comment: Quinolones are generally safe and effective, and one should not get totally freaked out by these reports. Every drug has hundreds of reported side effects (just look up acetaminophen in the *PDR*) that are coincidental but not necessarily causative to the drug in question. This is a relatively weak article, but there seemed to be a temporal relationship between standard

doses of levofloxacin and ciprofloxacin and generalized seizures. There are other similar scattered reports in the literature so I'll wager the concept is valid.

Quinolone-related seizures have to be relatively rare, and though it's academic to state that these drugs should be avoided in patients with the propensity for seizures or for those with known seizure disorders, this is not clinically possible or reasonable in many cases. I don't think there is any standard of care prohibiting quinolones for patients who have a seizure disorder documented, but there are often other antibiotics that will perform just as well, and perhaps they should be chosen instead. Many clinicians, including myself, have used quinolones for pneumonia in patients with alcohol withdrawal, low magnesium, and alkalotic blood without problems. That's a setup for a seizure if one buys the association. I wonder how many of those subsequently diagnosed with alcohol withdrawal seizure or delirium actually were subjected to some quinolone CNS toxicity.

I have seen numerous cases of confusion, delirium, downright weird mental status changes, restlessness, anxiety, and other difficult to explain neuropsychiatric symptoms in patients taking quinolones. My wife got truly wacky for an evening after a single Levaquin pill, and my daughter reported some very bizarre sensations, especially weird dreams. I am, therefore, a firm believer in the CNS-quinolone dysfunction concept. Most of the potentially suspect individuals have complicated medical conditions, are elderly, and have a slew of reasons for goofiness that cannot be ferreted out in the ED.

I recall one hospital employee who developed a first-time seizure after I prescribed two doses of Cipro for a UTI, hence my reluctance to use quinolones for simple cystitis. In fact, our hospital antibiogram reports that macrodantin is most effective for *Escherichia coli*, eclipsing the laboratory superiority of any quinolone, cephalosporin, or sulfa drug. I'm sure we all see many patients with drug-related problems, and simply miss the diagnostic boat. Considering the comorbidities and a pharmacopeia of pills in their pocket, it's difficult to know where one drug begins and the other ends as an etiology agent. A true scenario would likely be impossible to ascertain in a short ED visit.

For me, articles such as this one are consciousness-raising and cause me to be a bit more vigilant in assessing the many seizure patients I see every day. I now look at the medication list garnered by triage more closely in the slightly confused, agitated, or off-kilter mental status that I previously glossed over. In fact, I have been specifically asking about antibiotic use under such circumstances.

Note that last month's column highlighted the fact that fluoroquinolones were the single most common drug associated with adverse neuropsychiatric drug reactions in a report from general practitioners. (*Pharmacol Res* 2005; 51[3]:211.) You probably won't see many patients having a seizure after taking a quinolone, but you may see many elderly patients who are a bit confused, just not right to you, or otherwise not right to the family so keep in mind that a quinolone may be the culprit. As I stated last month, it's probably good advice to stop using quinolones for bronchitis (AKA a chest cold), sinusitis (AKA a URI), otitis media, or to otherwise pharmacologically placate a patient who is weaseling for an antibiotic for a viral illness.

Overview of Quinolone-Induced CNS Toxicity

Clinical Manifestations
- Most reactions are benign: headache, dizziness, mild confusion, and insomnia (1%-2%).
- Toxic effects include tremors, convulsions, acute delirium, psychosis, agitation, and paranoia.

Incidence
- True incidence is unknown, but serious reactions likely are quite rare because quinolones are generally safe and well tolerated.
- Severe CNS toxicity gleaned from isolated case reports and anecdotal experience.

Etiology
- Will likely occur with all quinolones.
- Pathophysiology unknown, but could be related to blockade of endogenous GABA neuroinhibition.

Clinical Characteristics
- May occur after a few doses or after prolonged therapy.
- Described with oral and parenteral preparations.
- May occur with standards doses, not an overdose phenomenon.
- Abates spontaneously in hours to days after withdrawal of quinolone.
- No specific antidote known, but may be ameliorated with benzodiazepines.
- No permanent morbidity described.

Predispositions
- Generally not well described, but may be more common with higher doses.
- Renal impairment can occur in the elderly or in those with underlying psychiatric disorders or seizure disorders.

Clostridium difficile Diarrhea: A New Hypervirulent Superbug?

In 2003, several hospitals in Quebec, Canada, noted a marked increase in C. *difficile*-associated diarrhea. When studied prospectively (*N Engl J Med* 2005; 353[23]:2442), about 1700 cases of this nasty hospital-acquired diarrhea were evaluated. Almost three percent of hospitalized patients contracted C. *difficile*, and the 30-day attributable mortality rate was a whopping seven percent. An aggressive toxin-eluting strain of the organism resistant to fluoroquinolones was rampant. Statistically quinolone and cephalosporin use were risk factors. Amazingly, 62 percent of patients in these hospitals had been prescribed a quinolone during their stay, more than any other class of antibiotic.

You don't want to get hospital-acquired C. *difficile* diarrhea these days. Previously a hassle, now hypervirulent C. *difficile* is a killer. It is the leading cause of nosocomial infectious diarrhea, and prior antibiotic use is the most common culprit. Illness ranges from mild disease to fulminant colitis, and can lead to necrotic bowel, colectomy, or death. C. *difficile* toxins (A and B) are known virulence factors, coded by genes in the bacteria. This new epidemic strain not only produced scads of A and B toxin, but it secretes the nefarious binary toxin, too. Laboratories usually test for one or both of these common toxins in the stool because simply growing the organism has little clinical relevance. A few normal people are asymptomatic carriers. In some cases, the organism can elaborate another toxin, termed binary toxin, which can wreak additional GI havoc and tissue destruction. In this study, the C. *difficile* organisms were resistant to all fluoroquinolones (also a new finding because past strains were susceptible), explaining the overgrowth and subsequent increased toxin production.

This superstrain of C. *difficile*, with its binary toxin, was implicated in the impressive increase of antibiotic-associated disease and the unusually high morbidity and mortality seen in this investigation. A similar strain has been reported in the United States and Europe.

Emergence of Fluoroquinolones as the Predominant Risk Factor for *Clostridium Difficile*-Associated Diarrhea

Pepin J, et al
Clin Infect Dis
2005:41(9);1254

This article caused our infectious disease department to recommend that the ED drastically reduce the use of fluoroquinolones because of a concern for a rampant increase in *C. difficile*-associated diarrhea. *C. difficile* diarrhea is real, not just an annoyance. It is a bad disease, and it can be fatal. It has reached epidemic proportions in hospitalized patients, generally attributed to the increased use of broad-spectrum antibiotics. *C. difficile* has recently changed in virulence, and can be associated with more severe disease than previously encountered. Transmission in the hospital, particularly among the elderly and immunocompromised patients, readily occurs. Doctors and nurses are the carriers, and using a brief alcohol gel splash does not rid your hands of the vector. The shortage of private rooms and the sole use of the alcohol-based hand washing that may not be effective for *C. difficile* may also be contributory. You have to use soap and water to get this bug off your hands. I don't know how you get it off your stethoscope.

In this report from Quebec, Canada, a publication that got everyone's attention, 55 percent of the patients with *C. difficile* diarrhea had received fluoroquinolones in the preceding two months. These patients also were commonly prescribed proton pump inhibitors, another suspected facilitator of the epidemic. Other broad-spectrum antibiotics such as cephalosporins, macrolides, and clindamycin were only intermediate risk antibiotics for *C. difficile*. When statistically evaluated carefully, proton pump inhibitors were not contributory in this study. These authors believe that administration of fluoroquinolones was the most important risk factor for *C. difficile* during this epidemic of a new hypervirulent strain of this GI pathogen.

Other obvious risk factors for C. *difficile* were noted in this report: advanced stage disease, comorbidities, duration of hospitalization, ICU stays, tube feedings, and simply being in the hospital. The number of patients with *C. difficile* in this study was quite impressive. Interestingly, historically cephalosporins and clindamycin have been associated with *C. difficile*, but the use of these antibiotics was dwarfed by fluoroquinolones in this study. About 25 percent of all inpatients, regardless of diagnosis, received quinolones, a rather remarkable testament to the popularity of these drugs. This recently described novel strain, causing a more severe diarrhea, is highly

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resistant to quinolones, further compounding the problem.

Spores of *C. difficile* can survive for months in a hospital environment. Traditional infection control measures are not totally effective in reducing nosocomial transmission. Keeping patients out of the hospital will reduce exposure. Eschewing antibiotics also will help. Those with a long duration of hospitalization are more susceptible. The judicious use of antimicrobial agents is probably the most important way to control nosocomial *C. difficile*. These authors believe that sparing the use of fluoroquinolones and using other antibiotics such aminoglycosides for UTI would be another way to attack this problem. They also suggest using ceftriaxone and azithromycin rather than monotherapy with levofloxacin for community-acquired pneumonia. Of course, shorter courses of antibiotics or no antibiotics at all for questionable cases also seem prudent.

Comment: There is no question that almost any broad-spectrum antibiotic can cause *C. difficile* diarrhea in hospitalized patients. This is yet another reason to forgo the use of antibiotics unless absolutely necessary. *C. difficile* is a bad disease. It can cause a raging colitis and an acute abdomen, get you a colectomy, and can be lethal, rapidly in the debilitated immunocompromised patient with multiple medical problems who is most likely to receive empiric antibiotics.

Since 2003, *C. difficile* infections have morphed into more a severe process, are more refractory to standard therapy, and are more likely to relapse than previously described. This was news to me, but it was a front-page story in the infectious disease community and infection control circles. No wonder the Joint Commission folks watched for hand washing as a priority. This bug is now truly biologically different and supercharged with toxin, and a new strain actually has emerged. A toxic megacolon is now not an uncommon result of an infection that used to be just really annoying.

Attempting to stop *C. difficile* transmission in the hospital is a prodigious task indeed, but that's exactly where most patients will contract this illness. It can, however, strike the otherwise healthy individual off the street, seemingly out of nowhere. I have seen a few cases of *C. difficile* diarrhea in healthy young patients who had none of the traditional risk factors, and were not on antibiotics at all. I have now added an assay for the *C. difficile* toxin when I send a stool sample for culture, although this test is not perfect and will miss some cases if only a single sample is sent. Remember, *C. difficile* diarrhea must be treated with oral antibiotics; intravenous metronidazole or vancomycin will not cure this process. Many of our inpatient physicians are now giving septic patients oral antibiotics specifically aimed at quelling *C. difficile* in the GI tract, not an easy task in a ventilated patient.

To give one final scary perspective, the carriage rate of *C. difficile* in the general population is about three percent, and again, this is news to me, but the carriage rate in hospitalized and long-term care patients is 20 percent to 50 percent, so just assume everyone has it. About 20 percent of those lucky enough to be negative on admission will pick up *C. difficile* in their colon during hospitalization. Not everyone who becomes colonized in the hospital will get diarrhea, and many of those who are already carriers will escape diarrhea if the clinicians can stop saturating them with antibiotics. But newly colonized patients are 22 times more likely to develop blatant *C. difficile* diarrhea than those previously colonized when you first see them. EMN

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November 2008

Questions:

1. Fluoroquinolones can cause generalized seizures, especially in the elderly and those with decreased renal function or electrolyte abnormalities.
   ☐ **True** ☐ **False**
2. CNS toxicity of fluoroquinolones is thought to be related to a decrease in GABA-ergic neuroinhibition.
   ☐ **True** ☐ **False**
3. Fluoroquinolones will have no adverse effect on cognition, behavior, concentration, or sleep patterns.
   ☐ **True** ☐ **False**
4. Fluoroquinolones are one of the leading antibiotics associated with *Clostridium difficile* diarrhea in hospitalized patients.
   ☐ **True** ☐ **False**
5. Alcohol gels used for hand disinfection will kill *Clostridium difficile* spores within seconds.
   ☐ **True** ☐ **False**

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