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. Quinolones are generally considered safe and effective, and one should not otherwise worry about their use, except for concerns about allergy 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.

**Release Date:** November 2008

**Adverse Reactions to Fluoroquinolones**

By James R. Roberts, MD

**Author Credentials and Financial Disclosure:** James R. Roberts, MD, is the Chair- man of the Department of Emergency Medicine and the Director of the Division of Toxicology at Mercy Health Systems, and a Professor of Emergency Medicine and Toxicology at the Drexel University College of Medicine, both in Philadelphia. 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.

In Philadelphia.

By James R. Roberts, MD

**Release Date:** November 2008

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### 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 tract 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 inceptive 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...
Overview of Quinolone-Induced CNS Toxicity

Clinical Manifestations
- Most reactions are benign: headache, diziness, 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.
- Abrates 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 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.

Emergence of Fluoroquinolones as the Predominant Risk Factor for C. 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 suspect 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

Continued on next page
RESISTANCE TO QUINOLONES

Fluoroquinolones

Continued from previous page

resistant to quinolones, further com-
ounding the problem. Spores of C. difficile can survive for
months in a hospital environment. Tradition-
al infection control measures are
not totally effective in reducing noso-
comial transmission. Keeping patients
out of the hospital will reduce exposure.
Eschewing antibiotics also will help.
Those with a long duration of hospital-
ization are more susceptible. The judi-
cicious 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 antibi-
otics such as aminoglycosides for UTI
would be another way to attack this
problem. They also suggest using ceftxi-
axone and azithromycin rather than
monotherapy with levofloxacin for com-

munity-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 hospi-
talized patients. This is yet another rea-
son 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
colecctomy, 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 a more 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 infec-
tion control circles. No wonder the Joint
Commission folks watched for hand
washing as a priority. This bug is now
true biologically different and super-
charged 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 trans-
mision 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, seem-
ingly 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 antibi-
otics; intravenous metronidazole or
vancomycin will not cure this process.
Many of our inpatient physicians are
now giving septic patients oral antibi-
otics 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 per-
cent 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 previ-
ously colonized when you first see
them.

FLUOROQUINOLONES

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sent to you within six to eight weeks of participation.

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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□ 5 □ 4 □ 3 □ 2 □ 1

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ence in the activity’s topical area? If No, please explain why not.
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