Peripheral Neuropathy in a Patient Taking Ciprofloxacin

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This case, strengthened by an unintentional rechallenge, adds to a growing body of anectodal evidence that the often prescribed ciprofloxacin may be associated with peripheral neuropathy.

Ciprofloxacin is a commonly prescribed antibiotic that is used to treat a wide range of bacterial infections and is the preferred prophylactic agent against anthrax. It is in the drug class known as fluoroquinolones, which act by selective inhibition of DNA gyrase and topoisomerase IV. Ciprofloxacin is well absorbed from the gastrointestinal tract; it has 50% to 85% bioavailability and minimal loss by first pass metabolism, and about 20% to 40% of it is protein bound. It is metabolized hepatically by the cytochrome P4501A2 enzyme system to active metabolites and excreted unchanged through the kidneys (40% to 50%) and feces (20% to 35%), with a half-life of four hours.[1]

Although there is anecdotal evidence of an association between fluoroquinolones, including ciprofloxacin, and peripheral neuropathy, this association has not yet been proven. Fluoroquinolones are well known to be neurotoxic—by inhibiting gamma-aminobutyric acid (GABA) receptors, they produce dose-related central nervous system excitation.[2] The drugs can lower the seizure threshold and induce psychosis,[2] and they cause such adverse central nervous system effects as dizziness, headache, restlessness, and seizure in 0.9% to 4.4% of patients.[3] In addition, in July 2008, the FDA required all manufacturers of fluoroquinolones, including ciprofloxacin, to add a boxed warning regarding the risk of tendinitis and tendon rupture in patients taking fluoroquinolones.[4]

Ciprofloxacin is well tolerated in most patients, however, and the majority of its adverse effects are mild and self-limiting. The most common of these effects are nausea (2.5%), diarrhea (1.6%), and abnormal liver function tests (1.3%).[1] In comparison to these more common adverse effects of ciprofloxacin and fluoroquinolones in general, peripheral neuropathy is not as well described.[1]

In this article, we present evidence pointing to an association between ciprofloxacin and peripheral neuropathy. We describe the case of a patient who developed symptoms of peripheral neuropathy after beginning a course of ciprofloxacin, experienced a cessation of these symptoms after completing the drug course, and experienced a return of the symptoms after a rechallenge. In addition, we describe evidence of an association between the drug and the condition that we found through a review of FDA MedWatch data, along with evidence that has been published in previous reports. Finally, we speculate on the possible mechanism of ciprofloxacin-associated peripheral neuropathy, and we describe the diagnosis and treatment of the condition.

INITIAL EXAM AND PATIENT HISTORY

A 62-year-old man reported to the medical toxicology service of a large medical center. The patient's primary care physician referred him to this service for evaluation of a suspected adverse reaction to prescribed ciprofloxacin. The patient had been experiencing symptoms of peripheral neuropathy intermittently for approximately two months. He had been evaluated by a neurologist already and the results of electromyography were consistent with mild sensorimotor peripheral neuropathy.

About two months earlier, the previously healthy patient was discovered to have an elevated prostate-specific antigen level of about 4 ng/mL (normal levels generally are defined as less than 4 ng/mL, although levels vary with age, gender, medication use, and inflammatory processes) and underwent a digital

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rectal examination. He was diagnosed with prostatitis and was prescribed oral ciprofloxacin 250 mg twice daily for 10 days. Several days into the course of his therapy, he began experiencing a "pins and needles" sensation in his lower legs and feet. After finishing this course of antibiotics, his paresthesias had improved. On return to his primary care physician, he was prescribed an additional five days of ciprofloxacin for continued prostate pain. His paresthesias returned, and now included a stocking-glove distribution to all his extremities and involvement of the perioral and periorbital areas.

At the time of toxicology evaluation, approximately 30 days had elapsed since the patient's last dose of ciprofloxacin. His prostate pain had resolved completely, and he reported an 80% improvement of his paresthesias. A review of the patient's medical history was significant for paroxysmal atrial fibrillation (which was well controlled without medication) and mild cervical and lumbar spinal stenosis. He reported being active and taking supplemental magnesium daily but no herbal supplements and no prescription medication prior to his ciprofloxacin course. The patient also reported no exposure to chemicals (although he was employed as an executive of a large consumer products company) or history of smoking or illicit drug use. His reported last alcoholic ingestion had been about two years ago. The patient's family history was negative for any neurologic diseases.

A comprehensive review of systems revealed no unintentional weight loss, fevers, night sweats, or other constitutional symptoms. The patient reported no cranial nerve symptoms, including visual symptoms, dysarthria, or vertigo. His only other reported symptoms were a vague, nonspecific pruritus on his right forearm and an occasional ache in his right arm and shoulder. His blood pressure was 152/102 mm Hg and he had a pulse of 65 beats/min and a respiratory rate of 18 breaths/min. He was afebrile. Physical examination revealed no distress, and his skin examination was unremarkable. Neurologic examination revealed no focal deficits, and cranial nerve testing was normal. His deep tendon reflexes were 2+/4+ bilaterally. No tremors, akasthesias, or rigidity were detected. The patient's sensation to light touch was grossly intact and his motor examination was equal, symmetric, and 5/5 in all extremities. No clonus, pronator drift, or ataxia were noted. Finger-to-nose and Romberg testing were normal and the Babinski reflex was down-going bilaterally.

Screening laboratory testing was completed about three weeks after the patients' evaluation by the toxicology service. Liver function studies, chemistry studies, and a thyroid panel all were normal.

The normal laboratory findings essentially ruled out thyroid disease, diabetes, and electrolyte abnormalities as potential causes of the patient's neuropathy. Since tests of his renal and liver function also were normal, these functions would not affect the metabolism or excretion of ciprofloxacin. In addition, his history and physical examination did not raise any suspicion for alcoholism, drug abuse, autoimmune disorder, occult paraneoplastic process, or exposures to toxins in the workplace that might produce neuropathies. The patient appeared reliable and adherent to his medication instructions, and it is doubtful that he ingested more than the prescribed dose of ciprofloxacin. As his only other medication was supplemental magnesium, the likelihood that his peripheral neuropathy resulted from a drug interaction was low. After we ruled out these common causes of the problem, and since significant improvement after discontinuation of the ciprofloxacin was seen, we concluded it was highly probable, by the Naranjo criteria (score = 7),[5] that the patient's neuropathy resulted from ciprofloxacin exposure.

TREATMENT COURSE

Since the patient no longer was taking ciprofloxacin and his peripheral neuropathy was resolving, no treatment was required. About one month after his toxicology evaluation, the patient was essentially recovered from the neuropathy.

ABOUT THE CONDITION

To investigate further the possibility of an association between ciprofloxacin and peripheral neuropathy, we reviewed FDA MedWatch data from November 1997 through March 2006 for adverse events associated with ciprofloxacin use.[6] We found a total of 7,282 reports, 338 (4%) of which documented peripheral paresthesia or polyneuropathies. Of these 338 reports, 281 (83%) listed ciprofloxacin as the primary suspect (Table).

A possible association between the drug and the condition was first reported in 1992,[7] and scattered reports have been published since then. A recent report discussed acute peripheral neuropathy in a patient with lupus whose symptoms resolved after discontinuation of ciprofloxacin. The patient did not have a lupus flare at the time of her peripheral neuropathy, and, although the temporal relationship suggested an association, a rechallenge was not undertaken.[8] Another report described 37 cases of fluoroquinolone-associated peripheral neuropathy—five of them involving ciprofloxacin—that were reported to the Swedish Adverse Drug Reactions Advisory Committee over a seven-

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year period. Most of these cases were mild and resolved after discontinuation of the fluoroquinolones.[9] In addition, a survey conducted through the internet in 2001 found 45 cases of peripheral neuropathies associated with fluoroquinolones. Eleven of the cases involved courses of ciprofloxacin, and 36 reported severe events.[10] Schering-Plough (Kenilworth, NJ), the distributor of ciprofloxacin, responded to concerns about the possible association by including peripheral neuropathy in the product labeling as a postmarketing adverse event in 2004.[11,12]

The anthrax bioterrorism incident of 2001 also led to some possible evidence of an association between the drug and the condition. The incident created an unprecedented, nationwide increase in prescriptions filled for postexposure prophylaxis in general and ciprofloxacin in particular.[13] Bayer HealthCare (Wayne, NJ), the manufacturer of the ciprofloxacin brand Cipro, disclosed a disproportionate increase in peripheral neuropathy and other neurologic symptoms, along with gastrointestinal and musculoskeletal symptoms, during the incident as compared to previously reported clinical trials. The manufacturer warned against any premature conclusions relating to any drug-related event, however, because its findings lacked a control group and were laden with multiple confounding factors.[1]

It is worth noting that there have been no reported cases of peripheral neuropathy in the pediatric population—which likely is due to the low prevalence of fluoroquinolone use in children. Data on the drug's long-term safety in the pediatric population is limited.[1] There are concerns about joint and cartilage toxicity, but this toxicity was discovered through juvenile animal studies, and a direct association is unclear.[14] Due to their excellent tissue penetration, low protein binding, and long elimination half-life, fluoroquinolones frequently are used selectively in pediatric patients.[14–16] The only approved pediatric indications for ciprofloxacin, however, are in complicated urinary tract infections (in which case the drug is not used as a first-line agent) and in postinhalational anthrax exposure.

Overall, while we lack the standardized clinical trials needed to prove an association between ciprofloxacin and peripheral neuropathy, we believe that our case, together with the other cases described here, offers convincing evidence for such an association.

Table. All cases of adverse peripheral neurologic effects with ciprofloxacin listed as a suspected agent, according to FDA MedWatch data, November 1997–March 2006

Reported symptom	Ciprofloxacin listed as primary suspect, no.	Ciprofloxacin listed as secondary suspect, no.
Paresthesia	97	17
Peripheral neuropathy	79	11
Hypoesthesia	70	17
Polyneuropathy	16	9
Guillain-Barre syndrome	10	2
Hyperesthesia	6	1
Mononeuritis	2	0
Neuritis/sciatica	1	0
Total	**281**	**57**

Possible mechanism of association

The exact mechanism of action that could lead to the development of peripheral neuropathy in certain patients using ciprofloxacin is unclear. The patient in our case and many of the patients in previous studies revealed similar axonal disease, as evidenced by biopsy reports or nerve conduction studies. This finding is consistent with the pathologic changes—primary axonal degeneration with secondary breakdown of myelin sheath—that previously have been seen in most drug-induced peripheral neuropathies.[17] In vitro studies using hepatic microsomes have demonstrated the production of free radicals in a dose- and time-dependent fashion. This finding of oxidative stress at the molecular level has been cited in medical literature as a suspected mediator of tissue destruction.[18] Because the cytochrome P4501A2 system exhibits genetic polymorphism and its expression is highly variable, the likelihood of an adverse event would be expected to be higher in patients who have a diminished capacity for biotransformation of the parent drug. This genetic polymorphism has not been linked directly to the development of peripheral neuropathy, however.[19]

Diagnosis and treatment

The diagnosis of ciprofloxacin-associated peripheral neuropathy is based on a history of exposure and subse-

quent neuropathic symptoms—usually within the first week of therapy, although reports of symptom onset after several weeks or even months of therapy exist.[7,9,10] If the findings are early and the diagnosis is still in doubt, nerve conduction studies and a biopsy may be beneficial.

The optimal treatment for the problem is cessation of ciprofloxacin. Although certain medications—including gabapentin, lidocaine, imipramine, carbamazepine, and even vitamins—have been used to treat peripheral neuropathy, there is no antidote for ciprofloxacin-associated peripheral neuropathy. Furthermore, it is possible that these remedies do nothing to alter the course of the underlying condition and may, in fact, be harmful. There have been reported cases of ciprofloxacin-associated peripheral neuropathy that have persisted or resulted in long-term disability, but it remains to be seen if this truly is due to a cause-effect relationship or if other factors may be involved.[10] Further well controlled studies in this area are warranted.

The index of suspicion should be heightened if peripheral neuropathy cannot be explained by reasons other than ciprofloxacin use.

IN SUMMARY

The prognosis for ciprofloxacin-associated peripheral neuropathy appears to be good if the potential drug-effect relationship is recognized early and the ciprofloxacin is discontinued. It is imperative that physicians educate their patients properly when prescribing ciprofloxacin and that they have a high index of suspicion when a patient taking the drug presents with symptoms consistent with peripheral neuropathy. These simple measures may prevent long-term sequelae and, possibly, irreversible nerve damage.

The index of suspicion should be heightened if peripheral neuropathy cannot be explained by reasons other than ciprofloxacin use or if there is a climate of increased terrorist threat. With regard to the later scenario, it is worth noting that a significant anthrax exposure would increase the number of prescriptions filled for ciprofloxacin, the number of erroneous uses of the drug, and, consequently, the incidence of ciprofloxacin-associated adverse events. ●

Author disclosures

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