Fluoroquinolone toxicity symptoms in a patient presenting with low back pain

Megan Strauchman, Mark W. Morningstar

Natural Wellness & Pain Relief Centers, Grand Blanc, MI, USA

Abstract

Fluoroquinolone medications have been shown to contribute to tendinopathies, cardiotoxicity, and neurotoxicity. Low back pain is a common musculoskeletal condition for which chiropractic treatment is most often sought. This case report details a patient presenting with low back pain and a history of fluoroquinolone toxicity. The patient was initially treated with chiropractic manipulation, which increased her symptoms. She was then referred to an osteopathic physician who treated the patient with intravenous antioxidants and amino acids, an elimination diet, and probiotic supplementation. Within 4 months of therapy, the patient reported a decrease in pain, a resolution of her dizziness, shortness of breath, panic attacks, tachycardia, and blurred vision. After an additional 8 weeks of antioxidant therapy, she reported further reductions in pain and improved disability. People susceptible to fluoroquinolone toxicity may present with common musculoskeletal symptoms. A past medical history and medication history may help to identify this population of patients. People presenting with fluoroquinolone toxicity may have unidentified contributing factors that predispose them to this anomaly. This patient reported improvements in pain and disability following antioxidant amino acid therapy for a total of 6 months. The natural history of fluoroquinolone toxicity is unknown and may account for the observed improvements.

Introduction

The incidence of adverse reactions to the fluoroquinolone class of medications has been given increased attention in recent literature. Fluoroquinolones are broad-spectrum antibiotics, including the most widely used of these which are ciprofloxacin, levofloxacin and moxifloxacin.[1] The most serious reactions caused by this class of medication include toxicities of the central nervous system, cardiovascular system, and the musculoskeletal system.[2,3] Annual emergency room visits due to reported adverse events from fluoroquinolones equals 9.2 per 10,000 prescriptions.[4]

Fluoroquinolone medications seem to cause musculoskeletal pain by three pathways, including inhibition of cell proliferation in tendons, inhibition of tenocyte migration, and increased matrix metalloproteinase expression, which induces collagen degradation.[5] This may account for an increasing number of primary care visits each year, since primary care visits at which a fluoroquinolone was prescribed increased from 7 million to 22 million between 1995 and 2002.[6]

It is conceivable that many of these patients are seeking help from complementary and alternative medicine (CAM) providers because of these potential musculoskeletal side effects, believing their symptoms are of a musculoskeletal origin. This report discusses a single patient encounter where her clinical presentation was consistent with fluoroquinolone toxicity. We discuss the history, diagnosis, treatment, and outcomes of this single patient case. We also discuss the potential ramifications this iatrogenic disorder has on primary care and/or CAM providers.

Case Report

A 38-year-old Caucasian female presented to our office in January 2011 with chief complaints of left-sided neck, arm and hand pain; left-sided mid-thoracic pain; and left-sided hip pain. She also reported left lower quadrant pain. Her symptoms began 6 years earlier (September 2005) following a therapeutic course of Avelox (moxifloxacin HCl) 500 mg daily for 14 days, for a sinusitis she had developed following a camping trip with her family. While taking this medication for the two-week period, the patient developed a progressively worsening set of symptoms. In addition to the chief complaints described above, she also developed episodic tachycardia, episodic dizziness, episodic shortness of breath, and chronically swollen glands. Additional symptoms included daily episodes of nausea, sweating, tremors, *brain fog*, blurred vision, panic attacks, and phonophobia.

She subsequently reported to a fibromyalgia clinic, where her lab studies showed hyperkalemia and elevated dehydroepiandrosterone sulfate levels, with no other remarkable findings. She was prescribed a multivitamin, broad-spectrum amino acid supplement, omega-3 fatty acid supplement, magnesium, and malic acid. She was also given Cytomel (liothyronine sodium). Over the course of the next three years she steadily improved. Although the patient stated that she experienced minor residual symptoms, her ability to perform her normal daily activities improved modestly (in her words).

Correspondence: Mark W. Morningstar, Natural Wellness & Pain Relief Centers 10683 S. Saginaw St Suite B, Grand Blanc, MI 48439 USA.
E-mail: drmorningstar@nwprc.com

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In November of 2010 the patient presented to the University of Michigan. Laboratory (lab) studies and a computed tomography scan of the brain ruled out Addison's disease, multiple sclerosis, lymphoma, and leukemia. The only abnormal finding was hypercalcemia. Following this consult she was given a diagnosis of clinical depression and fibromyalgia. She was prescribed Cymbalta (duloxcetine HCl) and referred for a psychiatric consult.

In January of 2011, prior to presentation to our office, she experienced an acute onset of severe lower left quadrant pain. After having the pain for three days, she went to her family physician. Her pain was diagnosed as a mechanical lumbar spine pain syndrome, for which she was given a corticosteroid injection. Obtaining no relief from her symptoms, the following day she went back to her family physician who diagnosed her with diverticulitis. She was prescribed ciprofloxacin 500 mg BID for 8 days and Flagyl (metronidazole) 500 mg daily. Over the course of this antibiotic regimen, she did not improve. She went to her gynecologist who found a left-sided ovarian cyst that had ruptured. Her left lower quadrant pain progressed to include the left coxa vera, left groin, and left sacroiliac joint. Over the following month she began to experience the previous symptoms she had shortly after her 2005 therapeutic trial, including panic attacks, insomnia, blurred vision, tachycardia, and nausea. This episode additionally included diffuse musculoskeletal joint pain. The patient also reported that her elbows, wrists, and knees *seemed to crack too easily and too often.*

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Intervention and outcomes

At this point in time she consulted us for these symptoms. She received chiropractic manipulation for articular dysfunctions in the left sacroiliac joint, lumbar spine, and left cervical spine. She completed a baseline quadruple numeric pain rating scale[7] and a functional rating index.[8] Her scores were 70 and 65% (26/40) disability. Manipulation increased the patient's symptoms local to the treatment later the same day the manipulation was rendered. Due to this, manipulation was discontinued and it was suggested to the patient that laboratory studies be completed first before attempting further manipulation.

The patient's history lead us to think that the patient was experiencing widespread chronic inflammation. Therefore, we ordered testing to help identify any underlying sources of chronic inflammation. A heavy metal toxicity urine challenge was ordered, along with the following laboratory studies: thyroid panel including thyroid peroxidase and thyroglobulin antibodies to rule out autoimmune hypothyroidism, salivary female hormone panel to evaluate estrogen metabolism, urine porphyrins, urine indican to assess intestinal dysbiosis, complete blood count, Chem 18, and anti-nuclear antibodies (ANA), titer (another autoimmunity screen). In our clinical experience, patients with fibromyalgia often display autoimmune tendencies. Therefore, these labs were ordered to try to identify the xenobiotic, xenoestrogen, or food sensitivities responsible for these autoimmune tendencies. These lab assessments provided the following results: elevated progesterone, low testosterone, elevated coproporhyrin III, elevated total porphyrins, speckled ANA screen (suggestive of autoimmune connective tissue disorder), multiple elevated immunoglobulin G (IgG) titers to dairy-based foods and gluten-based foods, and iron deficient anemia. With these findings, a follow-up genetic detoxification profile was ordered to evaluate the patient's detoxification pathways. This test revealed a genetic polymorphism in the cytochrome P-450 pathway, as well as genetic variations in the catechol-o-methyl transferase enzyme, the N-acetyl transferase enzyme, and the glutathione-s-transferase enzyme necessary for glutathione conjugation and phase II detoxification. These genetic variations may predispose the patient to accumulation of potentially harmful environmental toxins that might otherwise remain subclinical.[9] Therefore, the patient was also tested for polychlorinated biphenyls and other volatile solvents. We found the patient to have elevated levels of ethylbenzene, xylene, and the pesticide dichlorodiphenyldichloroethylene. Although these levels could indicate environmental accumulation, impaired detoxification pathways may make this accumulation more of a contributing factor.

By the time all of the above testing was completed, the patient began a course of intravenous (IV) nutrient therapy in April 2011. Each IV consisted of 10 mL of l-glutamine (30 mg/mL), 5 mL of D-Ribose (50 mg/mL), and 2 mL of glutathione (100 mg/mL) in a 250 cc saline drip over one h, which was given two times weekly. After three weeks, 3 mL of N-acetyl cysteine (NAC) 10% was added to the IVs. This was delayed three weeks to ensure patient tolerance to IV nutrient therapy. This regimen continued for an additional four months. By the end of the second week (after inclusion of NAC) the patient's resting tremors completely stopped, with a significant decrease in her daily pain level by the end of the fifth week of IV therapy. From the start of the therapy, the patient had been additionally instructed to eat a gluten, dairy, and soy-free diet, and she was prescribed an oral probiotic supplement (Designs for Health, Suffield, CT, USA) consisting of 5 billion-probiotic bacteria (*Lactobacillus* and *Bifidobacteria* species) daily. At the end of the four months of IV therapy, the patient reported a stated 30% reduction in her daily pain levels, with resolution of her dizziness, shortness of breath, panic attacks, tachycardia, and blurred vision. The IV therapy continued with 10 cc of L-glutathione (100 mg/mL) and 10 cc of Poly-MVA, a novel antioxidant compound that is used in patients with immune system dysfunction.[10] These were added to help immune system function, as antioxidant therapy helps to reduce chronic inflammation caused by incomplete tissue repair.[11] She continued this therapy on a once weekly basis for an additional 8 weeks. At this time the patient followed up and reported a Quadruple Visual Analogue Scale score of 37 and a disability rating of 35% (14/40).

The patient continued to experience periodic, temporary exacerbations in her pain levels. Therefore, the patient was recommended to continue a course of treatment on a reduced basis to mitigate these episodes and in attempts to prevent them.

Discussion

The most commonly discussed side effects of fluoroquinolone medications are those affecting the musculoskeletal system.[12] This is important for all clinicians because this family of antibiotics is very commonly prescribed. Back or joint pain may ultimately be aggravated by, if not caused by, these medications. However, this patient also had other non-musculoskeletal symptoms that seemed to resolve after the patient received a treatment that was designed to improve detoxification via improved methylation, inhibit autoimmune potential, and decrease systemic inflammation. While somatic symptoms are most reported, there are other published cases of non-somatic side effects including delirium,[13] Tourette's syndrome,[14] seizures,[15] and dermatologic reactions.[16]

Although there is no officially recognized *fluoroquinolone syndrome*, the patient represented here seems to fit that type of diagnosis. Fluoroquinolone medications may inhibit hepatic cytochrome p450, which would result in impaired detoxification of toxic elements and substances.[17] However, it is important to note that fluoroquinolones were the most commonly prescribed class of antibiotics as of the year 2002.[16] The adverse reactions described here previously reportedly occur in only a small minority of cases.[2] These may be under-reported, where these symptoms were viewed as separate and distinct symptoms. Another explanation is that patients who truly experience fluoroquinolone toxicity symptoms do so because they have comorbid impaired detoxification pathways that inhibit fluoroquinolone metabolism and excretion. In the patient presented here, we found that she had polymorphisms in specific methylation and acetylation enzymes that may cause poor detoxification and clearance of toxic elements.[9,18-20]

Limitations

It is unknown whether or not the patient's symptoms were caused by the fluoroquinolone medication. It is possible that her symptoms were at least aggravated by her genetically abnormal detoxification pathways outlined earlier. Additionally, her IgG food sensitivities may have contributed to a more pro-inflammatory environment, which might also explain the widespread joint pain with which she initially presented. At this point, the concept of non-musculoskeletal fluoroquinolone toxicity is poorly understood, and more data needs to be collected and published on this topic.

Conclusions

Due to the study design, we can draw only limited conclusions. In this patient, treatment of her symptoms by intravenous antioxidant therapy was followed by reported improvements in pain level and improved activities of daily living. Because this case was not controlled, it is not known whether the treatment directly resulted in the reported improvements, or if they were a product of placebo or natural history. More research needs to be done on the idea of fluoroquinolone toxicity beyond this class of medication's effects on musculoskeletal tissues.

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