Clinical Vignettes

Ciprofloxacin-Induced Tendinopathy of the Gluteal Tendons

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Fluoroquinolone-induced tendinopathy most commonly affects the Achilles tendon; however, involvement of several other tendons has been described. This is a case report of ciprofloxacin-induced tendinopathy of the gluteal tendons with MRI findings. An obese 25-year-old woman with no significant past medical history was diagnosed with acute pyelonephritis and was treated with intravenous ciprofloxacin. Shortly after her first dose of ciprofloxacin, she developed severe left hip pain and decreased range of motion. MRI of the hips showed bilateral tendinopathy of the gluteal muscle insertion. A diagnosis of ciprofloxacin-induced tendinopathy was made based on her MRI and a Naranjo score of 7. Ciprofloxacin was stopped and her pain quickly resolved. Fluoroquinolones cause tendinopathy in 0.14 % to 0.4 % of patients using these agents. Fluoroquinolone-associated tendinopathy is a serious adverse reaction that can affect many tendons and should be considered in any patient presenting with new musculoskeletal complaints and in whom there is a history of fluoroquinolone use within the preceding 6 months.

KEY WORDS: ciprofloxacin; fluoroquinolone; tendinopathy; tendon; gluteal.

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BACKGROUND

Fluoroquinolone antibiotics are commonly used to treat genitourinary, respiratory, intra-abdominal, skin and soft tissue infections because of broad-spectrum antibacterial coverage and excellent tissue penetration. Prescription of fluoroquinolones is frequent, and in 2010, they were the fourth most commonly prescribed antibiotic class, accounting for 12 % of all antibiotics prescriptions.¹ They are generally well tolerated, but there have been numerous reports of fluoroquinolone-induced tendinopathy. While most adverse reactions are mild and self-limiting, sequelae can include tendon rupture. The most common tendon involved is the Achilles' tendon. However, quadriceps, extensor pollicis longus, triceps epicondyle, patellar and rotator cuff tendinopathies have also been described.² The following is a

case report of ciprofloxacin-induced tendinopathy of the gluteal tendons in a patient supported by radiographic evidence.

CASE PRESENTATION

A 25-year-old Micronesian woman presented to the Emergency Department with 1 week of bilateral upper quadrant abdominal pain. Based on her clinical findings and urinalysis, she was diagnosed with pyelonephritis and acute kidney injury. Treatment with ciprofloxacin 400 mg intravenously every 12 h and intravenous fluid replacement were initiated in the Emergency Department. Approximately 24 h after her first dose of ciprofloxacin, the patient developed acute, severe pain that was localized predominantly to the lateral aspect of her left hip. Over the next 2 days, she developed similar pain involving her right hip. She described the pain as sharp, radiating to both knees and worse with movement. The pain was poorly controlled with opiates and was severe enough to prevent her from ambulating.

The patient had no significant past medical history including no prior renal dysfunction, childhood hip pain or injuries, arthritis, joint pain or mobility problems. Her family history was significant only for unspecified arthritis in her mother. She did not report any current or past alcohol, tobacco or illicit drug use. She denied any history of sexual activity and also denied taking any medications prior to hospitalization, including fluoroquinolone antibiotics and corticosteroids. She was sedentary and did not participate in any type of regular exercise.

Physical examination revealed an obese young woman in no distress at rest but in obvious pain with any movement of her lower extremities. She was afebrile with normal vital signs. She had exquisite tenderness on palpation of her greater trochanter bilaterally and moderate tenderness over the lateral aspect of her thighs and knees. Active flexion of both hips was limited to 45 degrees, extension to 10 degrees, abduction to 30 degrees, adduction to 10 degrees, internal rotation to 20 degrees and external rotation to 30 degrees. Passive range of motion was slightly improved. There was no evidence of rash and no warmth, erythema or swelling of her hips, knees or other joints. Palpation of the gluteal, quadriceps, hamstring and gastrocnemius muscles revealed no tenderness.

The etiology of the patient's hip pain was initially unclear. Her laboratory test results were significant for a leukocytosis, a

creatinine clearance of 50 ml/min and an elevated c-reactive protein of 23 mg/dl (reference range, 0.0-1.0 mg/dl) and erythrocyte sedimentation rate of >130 mm/h (0-10 mm/h). Plain radiographic films of her hips showed no evidence of femoral head avascular necrosis or osteonecrosis, hip dysplasia, stress fracture or osteoarthritis.

The patient was started on a course of nonsteroidal anti-inflammatory drugs and corticosteroids for presumed trochanteric bursitis. MRI of her hips was subsequently obtained and demonstrated inflammation bilaterally at the gluteal muscle insertion (Figs. 1 and 2). The Naranjo score (Fig. 3), used to determine the likelihood that an adverse reaction is caused by a medication rather than the result of other factors, was calculated to be 7, suggesting a reaction to ciprofloxacin was probable.³ She was diagnosed with ciprofloxacin-induced tendinopathy, and the ciprofloxacin and prednisone were discontinued and cephalexin was substituted for continued treatment of her pyelonephritis. The patient's pain resolved over the following 24 h, and she was able to ambulate without any pain and was discharged shortly thereafter. She was seen in the outpatient clinic 1 week following hospital discharge and had returned to her normal state of health with no hip pain and full range of motion bilaterally.

DISCUSSION

Fluoroquinolone-induced tendinopathy was first reported in 1983 in a patient receiving norfloxacin.⁴ Since that time, the FDA has received an increasing number of reports and

subsequently issued a black box warning in 2008 describing this potential adverse drug reaction.⁵ To our knowledge, there has been only one case report of possible fluoroquinolone-induced tendinopathy of the gluteal tendons.⁶ Tendinopathy occurs in 0.14 % to 0.4 % of patients using these agents.⁷ Although theoretically a class effect, the fluoroquinolones most commonly implicated are pefloxacin and ciprofloxacin. Risk factors for tendinopathy include age greater than 60, renal impairment, history of organ transplant and concomitant corticosteroid therapy. Additional associations have been observed in patients with rheumatic disease, gout, diabetes mellitus, hyperparathyroidism, participation in sports and hypothyroidism.²

The mechanisms by which fluoroquinolones cause tendinopathy are unclear, although experimental data suggest that interactions with tenocyte regulatory proteins may damage tendon structure, with apoptosis as the final event in the causal pathway.⁸ Clinical experience has shown that the severity of tendinopathy is usually proportional to treatment duration.⁹ Toxicological studies have confirmed fluoroquinolone-induced tendinopathy is a drug-induced dose-dependent toxic effect of these agents.^{10,11} Chhajer et al.¹² found Achilles tendon rupture occurring at a lower total dosage of ciprofloxacin than other tendon disorders, suggesting an idiosyncratic response to the drug in some patients.

As in our case, typical symptoms of fluoroquinolone-induced tendinopathy include sudden, sharp pain with palpation and movement of the affected extremity. This is usually associated with swelling, warmth, tenderness, erythema or pruritus over tendon attachment sites. Bilateral involvement

Figure 1. Coronal T2-weighted MRI of hips demonstrating abnormal fluid signal at the distal gluteus medius and gluteus minimus tendon attachments (arrows).

Figure 2. Axial T2-weighted MRI of hips demonstrating fluid tracking along the distal insertions of the gluteus medius and gluteus minimus tendons with more involvement on the left (arrows).

is common and may help to establish the diagnosis. Up to 50 % of patients develop tendon rupture with nearly one-third of these occurring in patients on concomitant long-term corticosteroid therapy. The average symptom onset is 2 weeks, but symptoms have been reported as early as a few hours after the initial antibiotic dose up to 6 months after stopping drug therapy.²

Our patient was substantially younger than the average patient with fluoroquinolone-induced tendinopathy (mean age, 59 years) reported in a recent review by Khaliq and Zhanel, which also found that males are more commonly affected than females, with an incidence ratio of 1.3-2:1.² Her symptoms developed more rapidly than commonly

reported, and her pain was initially unilateral, although it quickly progressed to involve both hips. Her acute kidney injury may have increased her risk of fluoroquinolone-induced tendinopathy. Of note, her ciprofloxacin did not require dose adjustment for her creatinine clearance. She lacked the other usual risk factors and had started taking corticosteroids after the onset of her pain. This is consistent with an idiosyncratic reaction. We submitted a report of this adverse drug reaction to the FDA's MedWatch.

The diagnosis of tendinopathy is a clinical one but can be supplemented with ultrasound, which can show tendon abnormalities that can be seen as hypoechoic areas, consistent with degenerative tissue and increased tendon thickness.¹³ As in

- 1) Are there previous conclusive reports of this reaction?
If YES = +1, NO = 0, Do not know or not done = 0
 - 2) Did the adverse event appear after the suspected drug was given?
If YES = +2, NO = -1, Do not know or not done = 0
 - 3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
If YES = +1, NO = 0, Do not know or not done = 0
 - 4) Did the adverse reaction appear when the drug was readministered?
If YES = +2, NO = -2, Do not know or not done = 0
 - 5) Are there alternative causes that could have caused the reaction?
If YES = -1, NO = +2, Do not know or not done = 0
 - 6) Did the reaction reappear when a placebo was given?
If YES = -1, NO = +1, Do not know or not done = 0
 - 7) Was the drug detected in any body fluid in toxic concentrations?
If YES = +1, NO = 0, Do not know or not done = 0
 - 8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?
If YES = +1, NO = 0, Do not know or not done = 0
 - 9) Did the patient have a similar reaction to the same or similar drug drugs in any previous exposure?
If YES = +1, NO = 0, Do not know or not done = 0
 - 10) Was the adverse event confirmed by any objective evidence?
If YES = +1, NO = 0, Do not know or not done = 0
- SCORING
- > 9 = DEFINITE ADR
 - > 5-8 = PROBABLE ADR
 - > 1-4 = POSSIBLE ADR
 - > 0 = DOUBTFUL ADR

Figure 3. Naranjo algorithm (designed by Naranjo et al., adapted by Doherty, M.)³. This figure was published in Respiratory Medicine CME, vol 2, Martin J. Doherty, Algorithms for assessing the probability of an adverse drug reaction, pp 63-67, copyright Elsevier (2009).

our case, MRI can identify tendinopathy or tendon rupture, which appears as gaps at the site of rupture, hyperemic torn tendon ends and fluid.¹⁴

At the first sign of tendon pain, swelling or inflammation, the patient should be advised to stop taking the fluoroquinolone drug and avoid exercise and weight-bearing on the affected limb for at least 2–6 weeks, sometimes as long as 6 months in Achilles tendinopathy.⁹ Nonsurgical interventions include analgesics, physical therapy, heel raise, cast or immobilization.¹⁵ Operative repair of tendon rupture is an option for patients who are candidates for surgery.⁹

Immediate improvement of symptoms on cessation of fluoroquinolones has been described and full recovery is usually expected within 1–2 months, although recovery can take as long as 20 months. Sequelae are reported in 10 % of cases and include swelling, bruising, difficulty walking, decreased range of motion and pain in addition to tendon rupture.² Patients should not be rechallenged with any fluoroquinolone as recurrence has been reported.¹⁶

CONCLUSION

Fluoroquinolones can cause tendinopathy, a serious adverse reaction that may affect more tendons than previously reported. Our report describes an unusual presentation of a young woman with ciprofloxacin-associated tendinopathy of the gluteal tendons with MRI findings. Fluoroquinolone-associated tendinopathy should be considered in any patient presenting with new musculoskeletal complaints and in whom there is a history of fluoroquinolone use within the preceding 6 months. These antibiotics should be prescribed with caution to patients predisposed to developing fluoroquinolone-induced tendinopathy.

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Conflict of Interest: The authors declare that they do not have a conflict of interest.

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REFERENCES

- Center for Disease Dynamics, Economics & Policy. Antibiotic Use and Resistance in the US at a Glance: 1999–2010. Available at: http://www.cddep.org/sites/cddep.org/files/resistance_map_infographic_3.jpg. Accessed May 10, 2014.
- Khalil Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis*. 2003;36:1404–1410.
- Doherty M. Algorithms for assessing the probability of an adverse drug reaction. *Respiratory Medicine CME* 2. 2009;2:63–67.
- Bailey RR, Kirk JA, Peddie BA. Norfloxacin-induced rheumatic disease [letter]. *N Z Med J*. 1983;96:590.
- Tanne JH. FDA adds “black box” warning label to fluoroquinolone antibiotics. *BMJ*. 2008;337:a816.
- Ganske CM, Horning KK. Levofloxacin-induced tendinopathy of the hip. *Ann. Pharmacother*. 2012;46:e13.
- Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother*. 2007;41:1859–1866.
- Sendzik J, Shakibaei M, Shafer-Kortin M, et al. Fluoroquinolones cause changes in extracellular matrix, signaling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. *Toxicology*. 2005;212:24–36.
- Zavraniecki L, Negrier I, Vergne P, et al. Fluoroquinolone induced tendinopathy: report of 6 cases. *J Rheumatol*. 1996;23:516–520.
- Williams RJ III, Attia E, Wickiewicz TL, et al. The effect of ciprofloxacin on tendon, paratendon, and capsular fibroblast metabolism. *Am J Sports Med*. 2000;28:364.
- Stahlmann R. Clinical toxicological aspects of fluoroquinolones. *Toxicol. Lett*. 2002;127:269–277.
- Chhajed PN, Plit ML, Hopkins PM, Malouf MA, Glanville AR. Achilles tendon disease in lung transplant recipients: association with ciprofloxacin. *Eur Respir J*. 2002;19:469–471.
- Astrom M, Gentz CF, Nilsson P, Rausing A, Sjobers S, Westlin N. Imaging in chronic Achilles tendinopathy: a comparison of ultrasonography, magnetic resonance imaging and surgical findings in 27 histologically verified cases. *Skeletal radiol*. 1996;25:615–620.
- Schweitzer ME, Karasick D. MR imaging of disorders of the Achilles tendon. *AJR*. 2000;175:613–625.
- Greene BL. Physical therapist management of fluoroquinolone-induced Achilles tendinopathy. *Phys Ther*. 2002;82:1224–1231.
- Muzi F, Gravante G, Tati E, Tate G. Fluoroquinolones-induced tendinitis and tendon rupture in kidney transplant recipients: 2 cases and a review of the literature. *Transplant Proc*. 2007;39:1673–1675.