CASE REPORT

Levofloxacin-Induced Bilateral Achilles Tendinopathy

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INTRODUCTION

The fluoroquinolones, a group of antibiotics with a broad spectrum of activity, are being used more frequently for the management of infections.[1,2] Although the fluoroquinolones are generally well tolerated, uncommon but serious complications have been reported.[3] Fluoroquinolone-induced tendinopathy is a debilitating but rare complication that is of particular concern. The incidence rate has been estimated at between 15 and 20 per 100 000 patients treated.[4,5] Until recently, case reports have implicated only the older fluoroquinolones, such as norfloxacin, ofloxacin, and ciprofloxacin.[5-9] To date, there has been just one report from North America of levofloxacin-induced tendinopathy.[10] We report a similar case and review the literature on fluoroquinolone-induced tendinopathy.

CASE REPORT

A 67-year-old man was admitted to hospital with increasing dyspnea of 1 week's duration. The history of the presenting illness included long-standing chronic obstructive pulmonary disease (COPD) with emphysema, diagnosed in 1997, for which he was receiving home oxygen therapy. The past medical history was remarkable for a history of smoking, 4 coronary artery bypass graft procedures, hypertension, lung cancer treated by resection of the left lower lobe in 1995, and recurrent pneumonia (3 episodes within the previous year).

Medications on admission included enalapril 10 mg bid, hydrochlorothiazide 25 mg daily, ipratropium 80 µg qid, ipratropium 20 µg + salbutamol 100 µg prn, fluticasone 500 µg bid, and prednisone 5 mg daily. The patient had been taking prednisone 5 mg daily for approximately 1 year. The patient reported no drug allergies.

On examination, the patient looked unwell and was leaning forward in the bed. Temperature was 36°C, blood pressure 140/75 mm Hg, heart rate 96 beats/min, and respiration rate 28/min. A review of systems was remarkable only for dyspnea and rhinorrhea with clear secretions.

Chest examination revealed no wheezes, crackles, clubbing, or dullness to percussion. Bilateral enlargement of the Achilles tendons was present, and they were sensitive when pressure was applied. Heart sounds were normal, and no edema was present. Laboratory results were remarkable for hyponatremia (sodium 121 mmol/L, normal range 135–145 mmol/L), renal insufficiency (serum creatinine 138 µmol/L, normal range 62–120 µmol/L) with a calculated creatinine clearance of 0.8 mL/s (about 48 mL/min), and elevated platelets (448 x 10^9/L, normal range 150–400 x 10^9/L), white blood cells (15.7 x 10^9/L, normal range 4.0–10.0 x 10^9/L), and neutrophils (14.5 x 10^9/L, normal range 2.0–7.5 x 10^9/L). The results of blood gas analysis on admission were as follows: partial pressure of oxygen 58 mm Hg, pH 7.43, partial pressure of carbon dioxide 38 mm Hg, and bicarbonate 25 mmol/L on 2 L of oxygen. Chest radiographs showed that the left hemidiaphragm was elevated posteriorly; the left lower lobe resection was also apparent. No pleural effusion or opacity was noted.

The patient was diagnosed as having a COPD exacerbation secondary to chest infection. The patient was started on levofloxacin 500 mg daily, the oral prednisone was increased to 50 mg daily, and the patient's other medications were continued. When he was questioned regarding past antibiotic therapy, he described symptoms of bilateral lower tendon pain associated with the use of levofloxacin, which had been prescribed 4 months previously for a respiratory tract infection. On the second day of that course of

levofloxacin therapy, the patient had begun to experience bilateral general soreness around the Achilles tendon. On the third or fourth day, pain had developed, along with significant bilateral swelling, to the point that walking and foot flexion became unbearable. Despite the onset of these painful symptoms, the patient did not consult his family physician and completed the prescribed 10-day course of levofloxacin therapy. The pain persisted for approximately 4 weeks after the levofloxacin therapy was finished. As a result of this information, levofloxacin for the current chest infection was discontinued, and the patient's COPD exacerbation was managed without the use of antibiotics.

DISCUSSION

The first case report associating a fluoroquinolone with Achilles tendinitis was reported for norfloxacin in 1983 by Bailey and colleagues.[11] Tendon rupture was first associated with ciprofloxacin use and was reported to the British Committee on Safety of Medicines in 1987.[12] By 1995, 84 cases of fluoroquinolone-induced tendinopathy had been reported, and by 1996 the United States Food and Drug Administration had issued a report of adverse events for fluoroquinolones.[13,14] Approximately 1000 cases of fluoroquinolone-induced tendinitis had been reported to the French drug surveillance agency by 1997[3] and the European literature contains more than 200 reports of cases of fluoroquinolone-induced tendinopathy, primarily involving pefloxacin.[6] In 1999, Lewis and colleagues[10] reported the first case of levofloxacin-induced Achilles tendinitis, and between January and June 1999, the Swiss Drug Monitoring Center was notified of 7 cases of fluoroquinolone-induced tendinopathy involving levofloxacin.[15]

The exact mechanism of this phenomenon remains unknown.[5,6,8,9] Histological studies are rare; however, the available information suggests that the drug or its metabolites may have a direct toxic effect on collagen. Vascular complications with ischemia have been proposed to cause tendon rupture. Mechanical stress also seems to play an important role in the development of fluoroquinolone-induced tendinitis.[5-10]

Fluoroquinolone tendinopathy is distinguished from other forms of tendinopathy by the abrupt onset of sharp pain that occurs spontaneously with walking or palpation. Marked tendon swelling is usually present, and the involvement is frequently bilateral.[5,6,10] The Achilles tendon is the site most commonly affected.[5-10] In a case series that reported 100 cases of fluoroquinolone-associated tendinopathy, the Achilles tendon was affected in 96 cases, and close to half of these cases had bilateral involvement.[16] It appears that tendons bearing high loads, such as the Achilles tendon, are more susceptible to fluoroquinolone-induced tendinopathy. Thus, mechanical stress may partially explain the high degree of Achilles tendon involvement.[5-7] Other sites affected include the quadriceps, the peroneus brevis (at the midlateral margin of the fibula), the extensor pollicis longus (on the posterior and lateral surfaces of the ulna and the interosseous membrane), and the long head of the biceps and rotator cuff tendons.[5,6] The average time to onset of symptoms is 2 weeks[6,7] (range 1 day to 3 months[5-7]).

Several factors have been shown to increase the risk of fluoroquinolone-induced tendinopathy. Long-term corticosteroid use and concomitant administration of corticosteroids with fluoroquinolones are well-recognized risk factors.[5,10] A review of reports of fluoroquinolone-induced tendinopathy revealed that 41% were associated with corticosteroid use.[6] Renal failure, end-stage renal disease, long-term hemodialysis, and renal transplant also significantly increase a person's risk of fluoroquinolone-induced tendinopathy.[5,6,15,17,18] Renal disease alone has been implicated in 12% of cases.[6] It is important to note that end-stage renal disease alone has caused spontaneous tendon rupture.[17] Age and mechanical stress are also significant risk factors.[5-7,10,15]

Fluoroquinolone-induced tendinopathies occur at normal doses and treatment duration.[5] However, the severity of the tendinitis appears to be proportional to treatment duration. Patients are at increased risk of experiencing tendon rupture after the third week of fluoroquinolone treatment.[5]

Treatment consists of immediately discontinuing the fluoroquinolone and resting the affected tendon.[5-7,10] With mild tendinitis, non-weight-bearing activity for 2 to 6 weeks may be a sufficient period of rest. However, if rupture of the tendon is suspected, the patient should be referred to an orthopedic specialist, as casting is required. Early and prolonged physical therapy is frequently required, particularly for elderly patients (60 years of age and older).[5-7,10]

Even with early diagnosis and appropriate management, tendinitis heals slowly.[5-10] The mean recovery time ranges from 3 weeks to 3 months, and complete recovery can be anticipated if the tendon has not ruptured. A range of 4.5 weeks to 6 months has been required for patients to recover from a tendon

rupture.[5,19,20] It is recommended that affected patients not be rechallenged with any fluoroquinolone.[5,6]

Fluoroquinolone-induced tendinopathy appears to be a class effect. Although this complication is rare, it is highly debilitating. As the role of fluoroquinolones continues to expand, the potential exists for increases in the incidence of fluoroquinolone tendinopathy. As a result, pharmacists should be familiar with this toxic effect.

References

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