

# Quinolone-associated tendonitis: a potential problem in COPD?

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**Background** Quinolones have traditionally had limited application in the area of community-acquired respiratory tract infections due to poor cover against *Streptococcus pneumoniae*. This trend is changing with the broader spectrum of newer fluoroquinolones. A rare serious side effect of fluoroquinolones is tendinopathy.

**Aims** This study describes two cases of levofloxacin-associated tendinopathy in patients with severe chronic obstructive pulmonary disease (COPD) and the implications and mechanisms involved are discussed.

**Conclusions** The finding of two cases of levofloxacin-induced tendinopathy in our patients suggests that the problem may be more frequent than previously considered. Patients with COPD treated with fluoroquinolones may have other risk factors for tendinopathy such as advanced age, corticosteroid use and renal impairment and merit vigilance for signs of tendonitis.

## Introduction

Fluoroquinolone antibiotics have been in use for over 20 years. In particular, they have been used for the treatment of Gram-negative sepsis and are well tolerated with a good safety profile.<sup>1,2</sup> However, their activity spectrum has tended to limit their use to hospitals and as a second line agent in the community.<sup>3</sup> A rare but debilitating side effect of fluoroquinolones is that of tendonitis, first reported in 1983 with norfloxacin but most frequently associated with ciprofloxacin, with a number of case reports in the literature.<sup>4,5</sup>

Recently, newer fluoroquinolone agents have been developed such as levofloxacin and moxifloxacin, with increased activity against Gram-positive organisms including *Streptococcus pneumoniae*.<sup>3</sup> Such an activity spectrum has increased their usefulness and they are now recommended by some authorities for both inpatient and outpatient management of community-acquired pneumonia and acute exacerbations of chronic obstructive pulmonary disease (COPD).<sup>6</sup> This will presumably increase the use of the newer quinolones in the population with COPD, particularly in primary care. Such patients may be older and frequently have concomitant steroid use, risk factors in themselves for tendonitis.<sup>4</sup> Two cases of levofloxacin-associated tendinopathy in patients with severe COPD are described and the implications and mechanisms involved discussed.

### Case report 1

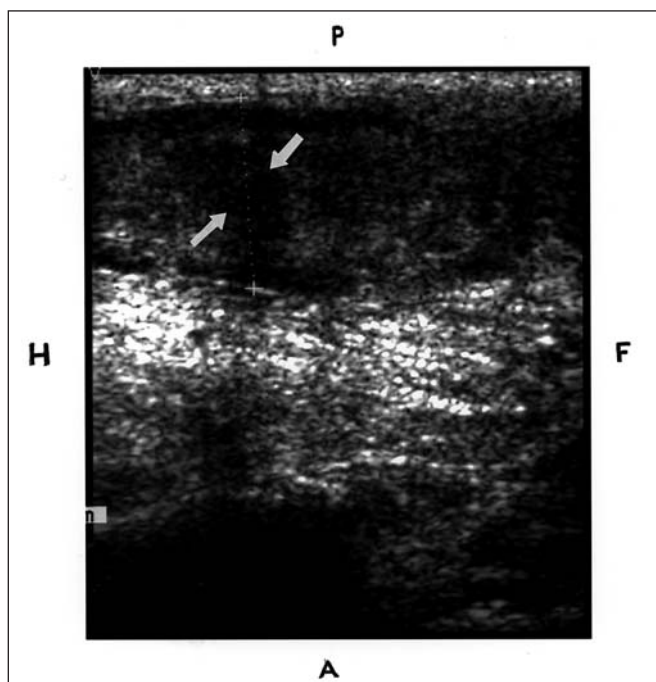
A 70-year-old Caucasian male with severe COPD (FEV1 35% predicted) presented in July 2000 with symptoms and signs of a mild acute infective exacerbation. He had been treated for pulmonary tuberculosis at the age of 28. He had no previous tendinopathy, renal failure or quinolone therapy and had no change in his medications for over a year. He had not been on regular steroid medication and had received occasional reducing courses of oral corticosteroids in the past.

He was commenced on a 10 day course of oral levofloxacin at a dose of 500mg once daily as an outpatient. Five days after completing the course of levofloxacin the patient began to complain of bilateral ankle pain. He was diagnosed with fluoroquinolone-induced tendonitis and underwent physiotherapy and ultrasound examination of his Achilles tendons that revealed bilateral rupture (see Figures 1 and 2). He was subsequently referred for surgical repair.

### Case report 2

A 55-year-old Caucasian male with a history of severe COPD (FEV1 18% predicted) presented in April 2000 with findings characteristic of an acute infective exacerbation. He had normal renal function and severe steroid-induced osteopenia and was undergoing assessment for possible lung transplantation. He had no previous tendinopathy and there had been no change to his medical therapy for the previous six months. In hospital he was treated conventionally with oxygen, nebulised bronchodilators, rapidly reducing intravenous and oral corticosteroids to zero and commenced on a 10-day course of treatment with oral levofloxacin at a dose of 500mg once daily. He was discharged after three days.

On the last day of treatment with levofloxacin he began to



**Figure 1.** Longitudinal ultrasound scan of left-mid Achilles tendon demonstrates significant tendon thickening (measuring 1.3cm; normal 0.4-0.7cm in thickness). There is altered echogenicity within the thickened tendon, (arrows) indicating tendon injury. P, posterior; A, anterior; H, head; F, foot.

notice pain in the Achilles tendon bilaterally. His symptoms got progressively worse over a period of two weeks to the extent that he had difficulty walking. His GP referred him for physiotherapy and an ultrasound examination of his Achilles tendons that out-ruled rupture. He steadily improved with rest, bilateral ankle-foot supports and oral non-steroidal, anti-inflammatory therapy. His symptoms resolved fully after a period of three months.

## Discussion

Quinolones have traditionally had limited application in the area of community-acquired respiratory tract infections where *S. pneumoniae* must be covered by any first-line antibiotic used for empiric therapy. This trend is changing with the emergence of the newer fluoroquinolones with their extended activity against such respiratory pathogens.<sup>3</sup> The incidence of quinolone-associated tendinopathy is unknown and difficult to evaluate given its rarity and the lack of prospective studies. In our review of the English language literature, there has been one previous report of levofloxacin-induced tendonitis<sup>7</sup> and reports have also been made to the manufacturer from post-marketing surveillance.

Pathologic mechanisms contributing to quinolone-induced tendinopathy are poorly understood. In vitro studies have demonstrated a direct effect of ciprofloxacin on fibroblast

metabolism, a marker of tendon function, in canine tendinous tissue.<sup>8</sup> Physiologic concentrations of the drug were shown to cause increased matrix degrading activity, decreased matrix synthesis and decreased fibroblast cell proliferation. These findings suggest a possible mechanism of fluoroquinolone-associated tendonitis. Histologic examination of biopsies of ciprofloxacin-associated tendinopathy reveal an inflammatory response similar to that observed in overuse syndromes involving the same tendons.<sup>9</sup>

Recognised risk factors for quinolone-induced tendinopathy include advanced age, corticosteroid use, previous tendinopathy and renal failure as quinolones are excreted renally.<sup>4</sup> The development of newer fluoroquinolones with a broader spectrum will increase their use in patients with COPD.<sup>6,10</sup> Increased age, steroid use and impaired renal function are found in this population and consequently such patients may have a higher incidence of tendonitis associated with quinolone therapy. The finding of two cases of levofloxacin-induced tendinopathy in our patients suggest that the problem may be more frequent than previously considered. Our series suggests that patients with COPD treated with fluoroquinolones merit particular vigilance for signs of tendonitis, as prompt cessation of the offending drug may presumably avoid the need for surgery.

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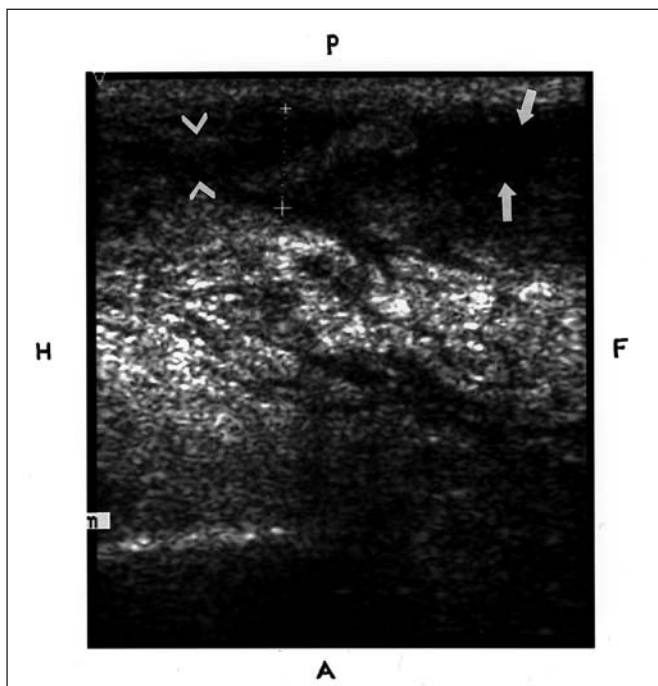


Figure 2. Longitudinal scan of right-mid Achilles tendon shows marked thinning of the tendon (between arrowheads) indicating an almost complete tear. Areas of decreased echogenicity (arrows) are due to haematoma. P, posterior; A, anterior; H, head; F, foot.

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