Fluoroquinolone-associated Tendinopathy

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The fluoroquinolones (FQs) are used to treat a wide range of infections because of their excellent gastrointestinal absorption, superior tissue penetration and broad-spectrum activity. Recently, FQ-associated tendinopathy and tendon rupture have been reported, especially in the elderly and patients with diabetes and renal failure. However, these adverse effects do not appear to be widely known among physicians. Because of the frequent use of FQs in clinical practice, physicians should be aware of their potential for severe disability from tendon rupture. Achilles tendinopathy or rupture is among the most serious side effects associated with FQ use, with reports markedly increasing, especially with the use of ciprofloxacin. The histopathologic findings include degenerative lesions, fissures, interstitial edema without cellular infiltration, necrosis and neovascularization. There are possible molecular mechanisms accounting for FQ-associated tendinopathy. First, ciprofloxacin mediates inhibition of cell proliferation and G2/M cell cycle arrest in tendon cells by down-regulation of cyclin B and cyclin-dependent kinase 1. Second, ciprofloxacin inhibits the spead and migration of tenocytes by down-regulation of focal adhesion kinase phosphorylation. Third, ciprofloxacin enhances the enzymatic activity of matrix metalloproteinase-2 with degradation of type I collagen. Management of FQ-associated tendinopathy includes immediate discontinuation of FQs, rest, non-steroidal anti-inflammatory drugs, physical modalities and eccentric strengthening exercise. Tendon rupture may require surgical intervention. *(Chang Gung Med J 2011;34:461-7)*

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The fluoroquinolone (FQ) class of antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin) has been used to treat a wide range of infections because of its excellent gastrointestinal absorption, superior tissue penetration and broad-spectrum activity.[1] The FQs are now recommended for treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis.[2,3] FQs can also be used to treat infections such as urinary tract infection, prostitis and sinusitis.[4]

FQs are considered to be relatively safe and well tolerated. The most frequently reported adverse events are gastrointestinal (1-7%), neurological (0.1-0.3%), cutaneous eruptions (0.5-2.5%), gait disturbance (1%), elevation of serum transaminases (1.8-2.5%), myalgia (< 0.4%) and althralgia (0.4%).[5-7] In

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addition, cumulated case reports indicate that FQs predispose to tendinopathy and even tendon rupture.

In July 2008, the Department of Health, Republic of China (Taiwan) issued a warning that FQs may induce tendinopathy or tendon rupture. However, physicians do not appear to be familiar with these adverse effects. Because of the frequent use of FQs in clinical practice and the potential for severe disability from tendon rupture, especially in the elderly, this article reviews the epidemiology, pathophysiology, molecular mechanisms, symptoms and signs as well as treatment regimens related to FQ-associated tendinopathy and tendon rupture. Physicians need to be reminded of this uncommon but potentially devastating adverse drug reaction.

Epidemiology

(Achilles) FQ-associated tendinopathy was first reported in 1983,[8] in a 56-year-old renal transplant patient who was treated with norfloxacin for a urinary tract infection with septicemia and subsequently developed Achilles tendinopathy. The first case of ciprofloxacin-associated tendon rupture was reported in 1987.[9] Since then, nearly 100 case reports and case-controlled studies related to FQ-associated tendon injury have been published.[10-12]

The mean age of patients with FQ-associated tendinopathy is 64 years, with a male-to-female ratio of 2:1, and 27-percent of patients have bilateral involvement.[13] The incidence of FQ-associated tendinopathy or tendon rupture in an otherwise healthy population is rarely reported, and is estimated to be 0.14% to 0.4%.[14-16] A study from the United Kingdom calculated the excess risk for FQ-associated tendinopathy at 3.2 per 1000 patient years.[17] The incidence of FQ-associated Achilles tendon rupture was estimated as 2.7 per 10000 patients for ofloxacin and 0.9 per 10000 patients for ciprofloxacin.[14]

Ciprofloxacin was reported to be the most common FQ in 90% of FQ-associated tendon disorders, with the risk of tendinopathy appearing to be dose independent.[18] Norfloxacin, ofloxacin, pfloxacin and levofloxacin have also been associated with tendon disorders.

Risk factors

The reported risk factors for FQ-associated tendinopathy and tendon rupture include systemic corticosteroid therapy, renal failure, diabetes mellitus, sports activity, history of musculoskeletal disorders and age over 60 years.[17,19,20] Forty-one percent of the reported patients concomitantly used corticosteroids. Some patients had been taking long-term oral corticosteroids. Others had recieved a corticosteroid injection within the past 3 days.[7,9,21-23] Furthermore, patients older than 60 years were at a 1.5-fold and a 2.7-fold greater risk for development of tendinopathy and tendon rupture, respectively, compared with patients less than 60 years of age.[10] End- stage renal disease was also postulated as a risk factor, since 12% of cases were associated with renal disease alone.[9,21,22,24] Other factors such as obesity, hyperlipidemia and hyperparathyroidism are well-known risk factors for tendinopathy or tendon rupture, and their risk potential is possibly exacerbated by concomitant FQ use.[10]

Pathophysiology

There are few reports of FQ-associated tendon injury in which histopathology was obtained. The pathologic features of degenerative lesions, fissures, interstitial edema without cellular infiltration, necrosis and neovascularization were demonstrated in a 68-year-old man who had been treated with pefloxacin for 3 months.[24] Abnormal fiber arrangement and structure with fibrotic areas, hypercellularity with rounded nuclei, neovascularization, and increased glycosaminoglycans in the extracellular matrix were seen. Necrosis has been noted in other patients who received norfloxacin and ciprofloxacin.[25,26] The mechanism of FQ-associated tendinopathy may be related to direct toxicity to the collagen because of the rapid onset of tendon injury.[21] It was reported that tendinopathy occurred hours after a single dose, which further supports direct cytotoxicity.[27,28]

Molecular mechanisms of FQ-associated tendinopathy

The exact mechanism of FQ-associated tendinopathy remains to be investigated. FQs act by inhibition of bacterial DNA gyrase (topoisomerase II) which is directly involved in DNA replication and cell division.[5] Animal studies have demonstrated disorganization of the extracellular matrix (ECM), inflammation of the paratenon and degenerative changes in tendon cells in fluoroquinolone-treated rats.[29,30] In addition, in a mouse model, pefloxacin

was demonstrated to induce a change in proteoglycan synthesis in the Achilles tendon.[31] Edema and increased mononuclear cells were noted in the tendon sheath of the Achilles tendon in a juvenile rat model.[31] The fluoroquinolone class of antibiotics has been documented to exert a number of effects on various cell types *in vitro*, including reduced expression of some ECM proteins,[18,27] decreased mitochondrial activity,[27] enhanced matrix metalloproteinase expression,[18,32-34] non-cytotoxic inhibition of tendon cell proliferation,[18,34] and inhibition of tendon cell migration.[35]

For the injured tendon, the healing process can be divided into three overlapping phases: (1) inflammation; (2) regeneration; and (3) remodeling and maturation.[36] In the regenerative phase of tendon injury, the tendon cells migrate into the repaired site and proliferate actively, and are responsible for the abundant deposition of ECM (mainly type I collagen) in the tissue.[37] In vitro studies have revealed possible molecular mechanisms of ciprofloxacin-associated tendinopathy. It was reported that ciprofloxacin mediated inhibition of cell proliferation and G2/M cell cycle arrest in tendon sells.[36] Furthermore, down-regulation of cyclin B and cyclin dependent kinase 1 as well as mitotic arrest with misaligned chromosomes and poor bipolar spindle formation were demonstrated in ciprofloxacin-treated cells. Down-regulation of check-point kinase 1 and up-regulation of polo-like kinase 1 may further account for the mitotic arrest. Meanwhile, ciprofloxacin inhibits tenocyte speading and migration in a process that is probably mediated by inhibition of focal adhesion kinase (FAK) phosphorylation.[36] It was also revealed that ciprofloxacin affected collagen metabolism by up-regulating the expression of matrix metalloproteinase-2 (MMP-2) in tendon cells at the mRNA and protein levels. Ciprofloxacin also enhanced the enzymatic activity of MMP-2 with degradation of type I collagen.[34] In addition, immunohistochemistry confirmed the increased expressions of MMP-2 in ciprofloxacin-treated tendon explants *ex vivo*. The cellular and molecular effects of ciprofloxacin on tendon cells are summarized in the Fig. 1. These findings indicate that ciprofloxacin exerts a negative impact on migration and proliferation as well as the collagen metabolism of tenocytes. Thus, ciprofloxacin might delay a tendon healing process that may be the cause of FQ-associated tendon injury.

Symptoms & signs

The clinical manifestation of FQ-associated tendinopathy is pain, typically of abrupt onset. Other symptoms include swelling, tenderness, and warmth or erythema over tendinopathic sites. The Achilles tendon is most commonly involved in FQ-associated tendinopathy, occurring in nearly 90% of cases.[38] Involvement of other tendons, such as the biceps

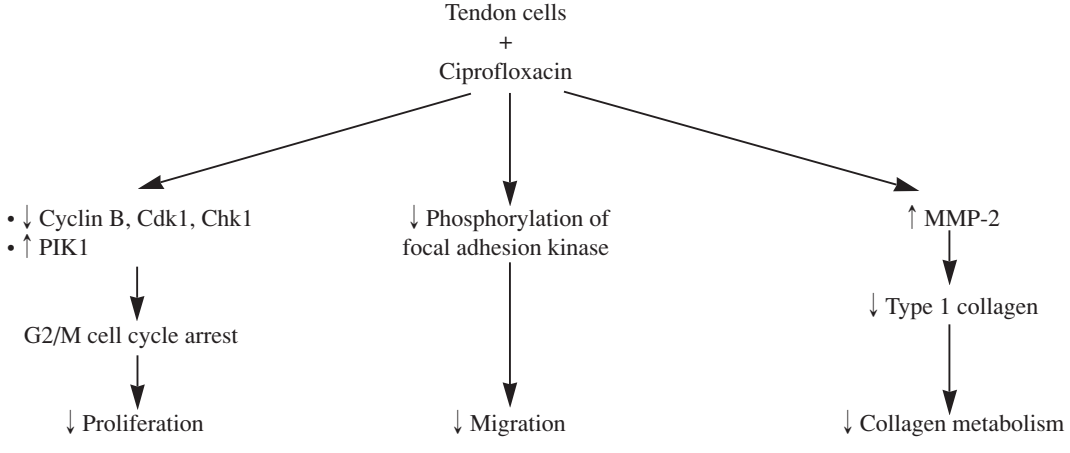

Fig. 1 The flow chart demonstrates the possible molecular mechanisms accounting for ciprofloxacin- associated tendinopathy or tendon rupture (↑ : up-regulation; ↓ : down-regulation). Abbreviations used: Cdk1: cyclin dependent kinase1; Chk1: check-point kinase 1; Plk 1: polo-like kinase 1; MMP-2: matrix metalloproteinase-2.

brachii, supraspinatus, extensor pollucis longus,[39] quadriceps,[23] peroneus brevis,[24] and epicondylitis has also been reported.[21] Some patients have bilateral involvement. Up to 50% of patients develop tendon rupture with nearly 30% of these patients concomitantly taking long-term corticosteroids.[19] It is noteworthy that nearly 50% of tendon ruptures occurred without warning.[20] Most tendon ruptures occur after 2 weeks of drug therapy. It should be emphasized that they can occur as early as a few hours after the initial dose or up to 6 months later, with a median duration of 6 days after FQ therapy.[10]

Diagnosis

A history and physical examination are essential to make the diagnosis. Patients with tendinopathy should be questioned about antibiotic use in the preceding 90 days.[28] Most reported patients presented within 2 weeks of initiation of therapy. Achilles tendon rupture can be diagnosed by Thompson's test (loss of plantar flexion when the calf is squeezed).

The diagnosis is usually clinical and may be confirmed by musculoskeletal ultrasound or, more precisely, magnetic resonance imaging (MRI). Ultrasonography is an inexpensive, radiation-free, easily available imaging modality that is commonly used to define tendinopathy or tendon rupture. Hypoechoic areas, consistent with degenerative tissue, and a thickened tendon are important sonographic features of tendinopathy.[39] MRI can also be used to identify tendinopathy or tendon rupture and can define the precise extent of involvement. It is also reported that MRI can classify tendinopathy and detect a risk of rupture.

Treatment

Treatment includes immediate discontinuation of FQ therapy at the earliest diagnosis of tendinopathy, rest and use of analgesics/anti-inflammatory medications.[40,41] Physical therapy including ultrasound diathermy, electrotherapy, taping and eccentric exercise can be added to the treatment regimen. Traditionally, rest was regarded as an effective treatment for tendinopathy. However, there has been a move toward early rehabilitation for tendinopathy in both operatively- and nonoperatively- managed tendon disorders.[42,43] In controlled trials, heavy-loading eccentric exercises improved tendon pain in the short term[44,45] and could lead to normalized tendon structure.[46] Weight-bearing restriction is applied for 2 to 6 weeks for mild tendinopathy. Tendon rupture can be treated conservatively by casting and prolonged rest or, more frequently, by surgery. Immobilization for 6 weeks to 6 months should be ensured.[7,27] Once FQ-associated tendinopathy is suspected, a patient should not be rechallenged with FQ.[27]

Recently, guidelines have been proposed for the use of FQ in athletes. First, athletes should avoid the use of FQ antibiotics unless no alternative is available. Second, oral or injectable corticosteroids should not be used concomitantly with FQ. Third, athletes, coaches and training staff should understand the potential risk of development of this complication. Fourth, close monitoring should be done for 1 month after completion of FQ use.[47] Physicians, athletes and coaches should follow these guidelines to prevent FQ-associated tendinopathy or tendon rupture in athletes.

Conclusion

FQ-associated tendinopathy should be considered in patients with musculoskeletal symptoms who have recently taken FQs. Discontinuation of the medication and immobilization of the affected joint should be immediately initiated once a diagnosis of FQ-associated tendinopathy is made. Patients' and physicians' awareness should be emphasized to reduce the morbidity associated with FQ-associated tendinopathy and rupture by prompting earlier diagnosis and treatment.

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氟化奎林酮類抗生素引起之肌腱病變

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氟化奎林酮類 (fluoroquinolone) 抗生素，因其有良好的胃腸道吸收率及組織穿透力，及其廣效性，此類抗生素廣泛被用於治療感染症。最近有許多報告指出氟化奎林酮類會引起肌腱病變或肌腱斷裂。其會造成老年人行動的不便及失能。然而臨床醫師對此問題並不熟悉，且因爲此類抗生素臨床上相當常用，所以本文特此強調。阿基里氏肌腱是最常發生肌腱病變的肌腱，尤其是使用環丙沙星 (ciprofloxacin) 之後。其病理組織顯示退化性病灶、裂痕、無發炎細胞浸潤之組織間水腫，組織壞死及血管新生。其可能的分子生物學機轉可能如下：一、環丙沙星會抑制肌腱細胞增生，並使細胞週期停留在 G2/M 期。二、此抗生素藉由降低局部粘黏斑激脢 (focal adhesion kinase) 之表現，會抑制細胞爬行及展開，三、並藉由促進第二型基質金屬蛋白酶的活性使第一型膠原蛋白分解。臨床上若遇肌腱病變的處理方式如下：停藥、休息、投予非類固醇發炎藥物，物理治療儀器及離心肌力強化運動等。若發生肌腱斷裂可能需外科手術治療。(長庚醫誌 2011;34:461-7)

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