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Review Article

Tendon Rupture as a Probable Side Effect of Ciprofloxacin: A Review Article

Nazanin Foroutan*

Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT

Ciprofloxacin is a broad-spectrum antibiotic from fluoroquinolones which are used to treat gram negative and positive bacterial infections. In last twenty years, tendinopathy is a worrying side effect. The side effects of tendon disorders including pain on tendon, angle tenderness, tendinitis and tendon rupture risk. Based on these symptoms various cases are shown and calculated. After several weeks pause in ciprofloxacin treatment the symptoms of tendon disorders are reduced.

Keywords: Ciprofloxacin; Antibiotic; Fluoroquinolones; Tendon rupture; Tendinopathy; Tendinitis; Side effects

INTRODUCTION

Ciprofloxacin is a broad spectrum antibacterial agent against gram negative bacteria and also gram positive (recently), anaerobic bacteria which belongs from the class of fluoroquinolones which are used for treatment of different bacterial infections ranging from urinary tract infections to respiratory tract infections [1-3]. It functions by inhibiting DNA gyrase and a type II topoisomerase, topoisomerase IV, necessary to separate bacterial DNA, thereby, inhibiting cell divisions [4-6]. Common side effects of fluoroquinolones are gastrointestinal effects (such as vomiting, nausea and diarrhoea), central nervous system reactions (from mild one such as sleeplessness, headache and dizziness to sever). Also Ciprofloxacin can cause skin tumors due to photosensitivity. Unlike other antimicrobial agents, fluoroquinolones have shown CNS effects (dizziness, headache, drowsiness, insomnia, organic psychosis and convulsions) as the second most frequently form of toxicity [7,8]. This might be due to the blood-brain barrier penetration or lipophilicity of fluoroquinolones [9-11]. Additionally, according to several case reports and investigations, tendinitis or tendon ruptures might be a probable side effect [12-14]. It is proved by laboratory tests and case reports.

The exact mechanism of ciprofloxacin in causing tendon rupture is not certainly determined. But the possible proposed mechanisms are effects of ciprofloxacin on expression of MMP-2,9, TIMP-1,2 and tissue inhibitor type I collagen in tendon cells and decrease in interleukin1-β [15,16].

METHODS

We searched in different databases like Google Scholar , PubMed, Science direct and Scopus using 'ciprofloxacin', 'tendon rupture' and 'tendonitis' as key words. All available articles related to these were included. The characteristics of reviewed articles or case studies have mentioned in Table 1.

CASE REPORTS

There are several case reports as following which are mentioned with the respect of low to high doses of Ciprofloxacin. Damuth, et al. reported a case that a woman suffered from kidney disease and consumes 250 mg ciprofloxacin per day for several days. This elderly person undergoes tendinitis which was improved after two days of ciprofloxacin cessation. He also concluded that fluoroquinolone should be used with caution in UTI especially in patients with advanced age and renal dysfunction [17]. Among all of the most important reports, a case report was about an old man who was administered 250 mg ciprofloxacin twice daily for his lower respiratory tract infection. After six days, he felt pain and snap on his calf which was the symptoms of tendon rupture, known after the examination [18]. Also, Karistinos and Paulos [19] revealed in the case report that a patient had taken a four weeks treatment for prostate infection with oral ciprofloxacin (800 mg/day). After 30 days completion of the treatment, complain was reported regarding the bilateral proximal anterior thigh deformity and also mild knee extension weakness in the year 2017.

Moreover, administration of ciprofloxacin 500 mg, i.e. twice a day, to a middle aged man with diabetes mellitus caused tendinitis with sharp pain sensation is a related case, reported by Mouzopoulos et al. [20]. Another interesting case was 32 years old man who suffered from Achill's tendon rupture in his right and left tendon

Correspondence to: Nazanin Foroutan, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran, E-mail- nfrootan.nazanin@gmail.com

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Table 1: The characteristics of reviewed articles or case studies list.

Author	Reason ciprofloxacin consumption	Duration of consumption	Amount of consumption	Other risk factors	Severity of tendino-pathy	Recovery
Muzi et al. [23]	Urinary tract infection	7 and 10 days	500 mg twice a day	Renal failure, hyperpara-thyroidism and corticosteroids	inter mediate	Two months
Damuth et al. [17]	Urinary tract infection	7 days	250 mg per day	Age	Intermediate	8 days
Ozaras, et al. [21]	Typhoid fever	10 days	500 mg twice a day	-	mild	-
Mouzopoulos et al. [20]	Pneumonia	7 days	500 mg twice a day	diabetes mellitus	sever	-
Akali and Niranjan [18]	Lower respiratory tract infection	7 days	250 mg twice a day	corticosteroids	sever	-
Movin et al. [22]	Osteomyelitis/ after surgery	12 weeks/7 days	500 mg twice a day	-	Intermediate	2 weeks

within one year interval of using 1000 mg ciprofloxacin orally for 10 days to treat typhoid; one month before the first incidence and repeat the same treatment for urinary infection one month before the second incidence [21]. The same problem was appeared in two other patients with consumption of ciprofloxacin with dosage of 1000 mg per day for one week in the first case and 1000 mg daily for 4 weeks which continued with 1500 mg for other 8 weeks in the second one [22].

Beside all these reports, Muzi et al. reported two cases of tendinitis and tendon rupture in kidney transplant recipients. The first one was a woman who received 500 mg twice a day for 10 days; after six months of transplantation for a urinary tract infection which leads to joint pain and edema after five days of treatment. These symptoms reversed one month later due to fluoroquinolones-therapy for recurrent Urinary Tract Infection (UTI). The latter one was a woman who received ciprofloxacin for 7 days. After that she experienced pain in Achilles tendon with edema [23]. Also other same reports strengthen the relative conclusion of tendinopathy with ciprofloxacin [2,24,25].

RESULT AND DISCUSSION

In-vitro surveys

To evaluate the aspects of mechanism of quinolone-induced tendotoxicity, a piece of tendon from a Caucasian patient was used. Monocytes were incubated by different concentrations (0, 3, 10, 30 and 100 mg/L) of ciprofloxacin for up to 4 days. Effects were investigated by electron microscopy and immune-blotting. The results show structural changes (like condensed materials in nucleus, swollen cell organelles and apoptotic bodies at the cell membrane which induced tendinopathy) by the concentration of 3 mg/L which were intensified by higher concentrations and incubation period [26].

Other cellular experiment was set in Taiwan in which cultured cells of Rat Achill tendon were left treat or untreated with 5, 10, 20 and 50 μg/ml ciprofloxacin. Several tests such as MTT assay, RT-PCR analysis, western blot analysis and gelatines zymography are used. The results shows that ciprofloxacin can have negative effects on tendon through the mechanism by up regulating gelatinase expression and it was confirmed by the evidence of increased degradation of type I collagen [15]. The same study was set up by human tendon fibroblast with 50 μg/ml ciprofloxacin which shows the ciprofloxacin can enhance the expression of MMP-1 and MMP-3 at not only the m-RNA but also the protein level [27]. Corps et al. used human tendon cell incubating with 50 μg/ml ciprofloxacin. After challenging with interleukin1-β for 48 hours, prostaglandin E-2 output was assayed. The way in which fluoroquinolones can causes tendinopathy may be the fact that ciprofloxacin decreases the interleukin-1β induced prostaglandin E-2 output in tendon cells [16]. Riley set an *in-vitro* study to determine the effect of ciprofloxacin on fibroblast metabolism. He incubated Achilles tendon, Achilles paratenon and shoulder capsule fibroblast in culture with 5, 10 and 50 μg/ml ciprofloxacin that resulted in 66-68% decrease in cell proliferation compare with control cells after 72 hours [28].

Pouzaud et al. from France set an *in-vitro* stress oxidative involvement experiment evaluating the toxicity of fluoroquinolones on tendon cells. Immortalized rabbit tendon cell line affected by fluoroquinolones was used to assess cell viability, redox status changes, reduced glutathione changes and reactive oxygen species production (with using Neutral red, Alamar blue, monobromobimane and 2,7-dichlorofluorescindiacetate fluorescent probes, respectively). Cold light cytofluorometer was used to analyze living tenocytes in which the fluoroquinolones showed moderate cytotoxicity after one day and more sever toxicity after another 48 hours. Interestingly, intrinsic toxicity with ciprofloxacin in comparison with other fluoroquinolones was high [29].

Statistical experiments

A survey during 1998-2000 in France on 525 pediatric patients who were categorize in to groups of control and patients who expose to fluoroquinolones using a pharmacy database revealed the fact that the relative risk of tendon and joint disorder with ciprofloxacin was 1.04 [30]. Similar experience in United Kingdom on 50000 patients shows the odd ratio of quinolones for Achill tendon rupture is 8.1; while, this ratio for current use of ciprofloxacin was 3.6% that age and consumption of corticosteroids increases the risk [31].

A case-control study in Italy during 2002-2003 investigated the tendon disorders with current use of fluoroquinolones. 22194 cases and 104906 controls had participated in this study. It was demonstrated that odds ratio of Achilles tendon rupture is around 2% which means it would occur for every 5958 patients treated by fluoroquinolones. The corresponding number in concurrent treatment with corticosteroids is 979 and 1638 for patient with age over 60 [32].

A study has evaluated 42 cases of tendon disorders in Netherlands

during the period of 1988-1998. It showed that the median period of latency between the use of fluoroquinolones and start of the first symptoms is 6 days and most recoveries had happened on average of 2 months after fluoroquinolones cessation [1].

During 2010 in Australia, Achilles Tendon Disease (ATD) was studied in lung transplant recipients. It shows 53% of Achilles tendon rupture was associated with the use of ciprofloxacin. But the relation was not dose related and Chhajed -the writer- concluded that the incidence may be idiosyncratic [33].

Risk factors

Some factors has mentioned which increase the risk of tendon injury in consumption of ciprofloxacin; age (over 60 years), renal failure, diabetes mellitus, organ transplantation, corticosteroids therapy or long history of diuretics treatment, hyperparathyroidism, rheumatic disease, gout, trauma, systemic lupus erythematous, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, long period of dialysis and Crohn disease [2,19,21, 23,31,34].

Evidence test

During 2011, Zargar set an experiment to determine whether platelet-Rich Plasma can protect tenocytes from effects of ciprofloxacin and dexamethasone. Five doses of ciprofloxacin (10, 20, 30 and 40 μg/ml) and 10-2 M dexamethasone exposed to cells for 3 days and after that cell viability was assessed by Alamar Blue. She substantiated that high dose of ciprofloxacin decreases tenocytes viability in comparison with controls whereas dexamethasone increases the senescent cells considerably [35].

Electron microscopy study

Shakibaei et el. have shown that there are various alterations in the microscopic structure of tenocytes between the control group and the groups treated with fluoroquinolones including dilatations, vesicles and vacuoles in the cytoplasm that had developed due to swellings of the rough endoplasmic reticulum. As an individual, the mitochondria have heavily damaged tenocytes that detached from the surrounding and extracellular matrix was detected in specimens which are treated with floroquinolones [36].

Comparison with other fluoroquinolones

An *in-vitro* survey has compared levofloxacin and ciprofloxacin activity and toxicity. In which, ciprofloxacin represents a higher intrinsic activity than levofloxacin with respect to the tendotoxic action [26]. While in other case study, 2539 tendon rupture were related to levofloxacin (61%), before ciprofloxacin (24%) and moxifloxacin (9%) where gemifloxacin, lomefloxacin and trovafloxan had the lowest risk of tendon rupture [37]. Besides, the possibility of tendon rupture for ofloxacin and ciprofloxacin are estimated as 2.7/1000 patients and 0.9/1000 patients respectively [38]. The number of reports for tendinitis and tendon rupture within two months of onset of therapy with norfloxacin was 3 per 1000 patients [39]. Among 421 cases from databases, 68% were attributed to pefloxacin, 18% were attributed to ofloxacin and 5% of them were for ciprofloxacin [40].

A study has analysed the 2235000 patients treated by mixofloxacin, among which there were no tendonitis [41]. Although ultra-structural changes have been shown in the Achilles tendons from immature rats treating with gemifloxacin, there are still no case reports available in human patients [42]. An *in-vivo* study was made on group of rats, among which ten are tested with fluoroquinolones, fleroxacin and pefloxacin caused lesions at a dose of 100 mg/kg of or more and lomefloxacin, levofloxacin and ofloxacin induced tendon lesion at the dose of 300 mg/kg while sparfloxacin and enoxacin has the same effect at the dose of 900 mg/kg or more. It is interesting to note that in this experiment three of those fluoroquinolones (norfloxacin, ciprofloxacin, and tosufloxacin) had no effects on Achilles tendon even at the high dose of 900 mg/kg [43].

In conclusion, *in-vivo*, *in-vitro* and structural surveys have shown that florouquinolones especially Ciprofloxacin can cause tendon rupture and tendinitis. Although it is not still clear which floroquinolones is the most riskful one in tendon disorders, it has been indicated that the risk of tendon disorders by ciprofloxacin treatment is not deniable.

CONCLUSION

After all, this review illustrates that ciprofloxacin has some negative effect upon tendon structure. In all presented cases several days or weeks after ciprofloxacin treatment cessation, improvement has appeared.

Besides, Ciprofloxacin has shown apoptotic impression on tendon cells in *in-vitro* experiments. Alteration in tendon structure ranging from development of swollen cell organelles and apoptotic bodies to degradation in interleukin-1β after ciprofloxacin consumption is evident.

Tendinopathy is not entered to the text books as ciprofloxacins' side effect possibility is around 3.5%. So, it is important to have more studies in this field and aware doctors and specialist to prescribe ciprofloxacin with caution especially in risky cases since drug safety is one the most important debates nowadays; drugs with health threating effects on patients should be substituted by more safe drugs. Studies have shown that with new floroquinolones, no case report of tendon disorders has been presented and more data about this subject needs more precise study [37].

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