

# Fluoroquinolone (Levofloxacin) Induced Tendinopathy with Partial Tearing of the Achilles Tendon -A Case Report

Amit Sharma<sup>1\*</sup>, Ashish Baldi<sup>2</sup>, Dinesh Kumar Sharma<sup>3</sup>, Ranbir Singh<sup>4</sup>, Durgadas Anghore<sup>4</sup>

<sup>1</sup>Research Scholar, Uttarakhand Technical University, Dehradun, Uttarakhand, Associate Professor, Department of Pharmacy Practice, ISF College of Pharmacy, Punjab, India

<sup>2</sup>Professor, Department of Pharmaceutical Science and Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab, India

<sup>3</sup>Principal, Devsthal Vidyapeeth College of Pharmacy, Dehradun, Uttarakhand, India

<sup>4</sup>ISF College of Pharmacy, Punjab, India

\*Corresponding author: Amit Sharma, Research Scholar, Uttarakhand Technical University, Dehradun, UK & Associate Professor, Department of Pharmacy Practice, ISF College of Pharmacy, Moga, (Punjab) India Tel: +919418783145; E-mail: [choice.amit@gmail.com](mailto:choice.amit@gmail.com)

Received date: 11 Oct 2017; Accepted date: 22 Nov 2017; Published date: 28 Nov 2017.

Citation: Sharma A, Baldi A, Sharma DK, Singh R, Anghore D (2017) Fluoroquinolone (Levofloxacin) Induced Tendinopathy with Partial Tearing of the Achilles Tendon -A Case Report. J Clin Case Stu 3(1): doi <http://dx.doi.org/10.16966/2471-4925.157>

Copyright: © 2017 Sharma A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

Adverse drug reactions (ADRs) are one of the key reasons for illness and death. For many years levofloxacin is known for its safety and unlike lines to cause ADR's. Tendinopathy is a rare complication that was documented and reported in adults as potentially serious and which can enhance the possibility of tendon rupture. Achilles Tendinopathy is a rare adverse effect of levofloxacin. This case report introduces a 78-year-old man diagnosed with partial tearing of Achilles tendon due to consumption of levofloxacin and drug methylprednisolone for treatment of chest infection and associated symptoms such as severe cough, breathlessness and wheezing sound. The assessment of ADR with Naranjo score was conducted and shows seven for this patient; accordingly, levofloxacin was the probable cause of this reaction. Early diagnosis of levofloxacin associated Achilles Tendinopathy and stopping the treatment may prevent tendon rupture. Food drug administration department also issued a cautionary warning specifying that fluoroquinolones, mainly levofloxacin can cause tendinopathy and tendon rupture in all ages patients. This possibility of risk of ADR's is furthermore increased in older patients generally over 60 years of age.

**Keywords:** Levofloxacin; Tendinopathy; Achilles tendon; Drug allergy; Adverse drug reaction

**Abbreviations:** Chronic Obstructive Pulmonary Disease-COPD; Adverse Drug Reaction-ADR; Intravenous-IV; Once A Day-OD; Two times a day -BSD, Food and Drug Administration-FDA, Injection -Inj., Tablet-Tab; Immediately-STAT; Peripheral Capillary Oxygen Saturation-SPO<sub>2</sub>, Acid Fast Bacilli-AFB; Tuberculosis-TB, Total Leukocyte Count-TLC, Erythrocyte Sedimentation Rate-ESR.

## Introduction

Adverse drug reactions (ADRs) are one of the key reasons for illness and death [1]. For many years levofloxacin is known for its safety and unlike lines to cause ADR's [2]. Fluoroquinolones such as levofloxacin have a broad range of antimicrobial properties as compared with older substances but have a similar safety profile [3]. The role of fluoroquinolones to induce and cause tendinitis and even tendon rupture is well recorded [2,4,5]. The first case of tendinopathy caused by fluoroquinolones was reported in 1983 on a patient receiving Norfloxacin. After this case the Food drug administration department has come to know many reports on this similar reaction and finally they issued a warning letter to healthcare professionals in 2008 in this regards [3,6]. As per our information and data available online, only few cases of probable and possible fluoroquinolone induced tendinopathy are recorded and reported in North India specially in Punjab.

## Case Report

A 78-year-old man visited the local hospital with complains and symptoms of breathlessness and febrile illness which was a known case of COPD and type -II diabetes having a history of severe cough from last 6 days. During the examination of this patient it was found conscious with no history of hypertension, BP-130/70 mmHg, heart rate 101/min., SPO<sub>2</sub>-95%, P/A- soft/non tender, respiratory rate- 20 b/min. and body temp- 99

F. Social history of the patient revealed that he was chronic smoker for the last 15 years. Lab investigation tests were conducted which contain sputum for AFB (*Acid-Fast Bacilli*) test was done for tuberculosis (TB) and found to be negative, hemoglobin 12.7 gm, random blood sugar (RBS) 245 mg/dl, total leukocyte count (TLC)- 3100/cmm which indicates decreased WBC count i.e. leukopenia, lymphocytes 22%, monocytes 01%, total RBC count 5.11 million/cm, troponin T or troponin- I proteins was found negative, erythrocyte sedimentation rate (ESR) 46mm/1<sup>st</sup>hour which indicates that there were many causes that can cause high ESR rate in the body which include allergic reactions too. Chest radiography was also performed which confirms pulmonary edema in patient.

For different complaining of an illness he was prescribed Injection (Inj.) Tazofast (*Piperacillin and Tazobactam*) 4.5gm in 100 ml normal saline (N.S) through intravenous- two times a day(IV-BD), Inj. Levoflox (Levofloxacin) 500 mg through intravenous- once times a day (IV- OD), Inj. Rab. (Rabeprazole) 20 mg IV- OD, Inj. Emset (Ondansetron) 4 mg IV- BD, Inj. Deriphyllin 1 amp. (2 ml) OD, Inj. Neodrol (Methylprednisolone) 125 mg in 100ml NS IV -OD, Nebulization with duolin and budocort4 hourly and Glumet tab. (Metformin) 500 mg OD. Patient was symptomatically better after the first day of treatment.

On the second day typhoid test was conducted for findings of immunoglobulins IgG&IgM antibodies in typhoid fever which was found

to be positive. On the second day same treatment was followed except Inj. Tazofast which was excluded from the therapy. Furthermore Inj. Optineuron I amp. 3ml IV- OD in 100ml of NS and Inj. Monocef 1.5 gm IV-BD were included in the treatment.

On the fifth day route of administration of levofloxacin was changed from IV to oral 500 mg tablet. On the sixth day, the patient reported mild pain in the right ankle and tenderness of right leg which continued throughout the week. Intensity of pain gradually increased while walking. The same treatment was carried out for next whole week. In physical exam, there was a local tenderness on posterior area of the right ankle, the lower one-third of right Achilles tendon, with reduced range of motion. On examination it was found that there was no swelling, warmth or skin color change on the painful region or around it.

Inj. Voveron (diclofenac) 75 mg IV stat followed by SOS was added to the treatment for pain in right ankle and tenderness of right leg. The Patient was symptomatically better. Two days later, the patient developed edema and complaint about severe pain of the right ankle and tenderness of Achilles tendon with a sharp pain extending to the right calf muscle. Other physical examinations were normal. Thus, Levofloxacin related Achilles tendinopathy was purposed as the impression so levofloxacin 500 mg oral and methylprednisolone were then discontinued. On follow up the patient reported that the pain subsided after drug exclusion from therapy and when placebo therapy was initiated.

The patient was provisionally diagnosed with tendinopathy until an ortho review was made on. Looking at the signs and symptoms of the patient, ultrasound of the right leg was conducted. The ultrasound report revealed that tendon thickening (1.5cm) with abnormally hypo echoic area closed to calcaneal insertion and grade 1 tendinopathy which confirmed partial tearing of Achilles tendon. Patient was advised not to bear weight on his right leg and physical therapy was assisted on regular basis. Further ortho consultation surgery was made while keeping blood glucose levels of less than 150 mg/dl.

The assessment of ADR with Naranjo score was conducted which shows seven for this patient; accordingly, levofloxacin was the probable cause of this reaction [7] (Table 1). The drugs which were prescribed in this case other than levofloxacin were found rational are Tazobactam is used in the treatment, control and prevention of respiratory infection. Rabeprazole act as gastro-resistant and used to suppress gastric acid production for a number of medical uses whereas Emset inj. is used for the treatment of nausea and vomiting, Deriphyllin inj. is used to prevent and reverse bronchospasm related with asthma, chronic bronchitis, emphysema, other obstructive airway diseases and metformin is used to treat type 2 diabetes.

The Naranjo scale was used to categories the probability of ADR or adverse event is related to drug treatment based upon a list of weighted questions [8]. Drugs are assessed individually for any causality, and score deducted if another reason may have caused in the adverse event, thereby failing the causal association [9].

Tendinopathy is a rare complication which was documented in adults is potentially serious which can surge the danger of tendon rupture [10,11].

## Discussion

The Food drug administration department also issued a cautionary warning specifying that fluoroquinolones, mainly levofloxacin can cause tendinitis and tendon rupture in all ages patients [12,13]. This possibility of risk OD ADR's is furthermore increased in older patients generally over 60 years of age, as well as in patients who were on corticosteroid drugs mainly for COPD, asthma, chronic bronchitis, emphysema, and in patients with renal, cardiac and respiratory related transplants [14]. Age and use of corticosteroid are the two main concurrent factors that may enhance the risk of tendon rupture which can also involve strenuous somatic movement, renal dysfunction, and previous tendon condition such as RA [15]. If further treatment is suggested surgical repair is the most recommended treatment for this ADR's of the Achilles tendon [15]. Tendinopathy and tendon rupture in the shoulder, hand, biceps, thumb, and other tendons have also been also reported [4]. Tendinopathy and tendon rupture also have been recorded and reported in patients who were on the treatment of levofloxacin [7,16]. Tendon rupture can happen throughout or after the end of therapy [17,18].

In the literature it was found that there is a risk tendon rupture of 1.7-fold for all tendinopathies, whereas 1.3 to 4.1-fold increase of Achilles tendon rupture and 46-fold increase of tendon rupture if the patients is on corticosteroid Treatment Therapy, Chances Of Tendon Rupture Increases 1.5-Fold If Patients Age Is Above 60 Years [4].

## Mechanism

The mechanisms by which fluoroquinolones causes tendinopathy are unclear and blurred, but the data obtained from previous experimental studies suggest that there are likely interactions with regulatory proteins in tenocytes which are responsible for causing damage to tendon structure and in conclusion leading to apoptosis in the causal pathway [19]. Several studies such as toxicological studies of levofloxacin confirm that this type of ADR's is related to drug induced and dose dependent toxic effect of these agents [20-22]. The Achilles tendon is major one which is affected most in 95% of cases of fluoroquinolone induced tendinopathy and ruptures which also affects the weight bearing properties due to injury [23].

**Table1:** The Naranjo adverse drug reaction (ADR) probability scale

The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered ?	+2	-1	0	-1
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	+1
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
<b>Total</b>				<b>+7</b>
Score of probability category: Definite=9 or greater, Probable=5-8, Possible=1-4 and Doubtful=0.				

## Management

In this case causative drug levofloxacin and participating drug answerable for worsen the case methylprednisolone were stopped and patient were advised to go for surgery as per orthopedics recommendations. As per guidelines, different studies and previous reports the management of immediate relief of symptoms of acute Achilles tendinopathy includes rest, use of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics as well as application of cold ice on affected area and heel lifts (orthotic devices used on both sides to prevent a gait imbalance) [24]. The treatment should be followed for 7-10 days, if no improvement observed after rest and NSAID's than gentle stretching and eccentric heel drop exercises are recommended, for treatment of Achilles tendinopathy [25,24]. Topical application of glyceryltrinitrate can be used for six months which may be effective but not more than exercise [18]. Open surgery and casting is an another option for resistant Achilles tendinopathy [26,27]. MRI may be useful in detecting and diagnosing tendinopathy [28]. Minimally invasive operative treatments include tendon stripping or percutaneous tenotomy [15].

## Conclusion

This is the first published case of possible levofloxacin induced partial Achilles tendon rupture in a patient suffering from COPD with other co morbidities in India, Punjab. This case illustrates the importance of avoiding levofloxacin in patients with known risk factors that have been discussed. Levofloxacin should be withdrawn if the patient feels pain, swelling, inflammation or rupture of a tendon. Patients should be advised to take rest if first sign softendinopathy are observed and physician should be informed to stitch the therapy of levofloxacin. Primary diagnosis of levofloxacin associated Achilles tendinopathy and stopping the treatment may prevent tendon rupture. It is important to be vigilant about diagnosis of Achilles tendinopathy. Accordingly, it is realized that the drug ADR may have various clinical presentations, which may be completely different from the expected pharmacological results.

Two important messages arise from this case study. Firstly, physicians should be cautious and careful while prescribing fluoroquinolone (levofloxacin) where the risk of tendon rupture is high. Of these, age and respiratory disease like asthma and COPD are the most important if patient is on corticosteroids therapy [29]. Secondly, antibiotics should be chosen based upon the most likely patients and test should be performed to identify the type of patient so that suitable and appropriate antibiotics can be prescribed [30,31].

Thus, it is practical and critical that the physicians always considers the drug adverse effects in disease diagnostic approach and these antibiotics drugs should be prescribed with more caution to patients susceptible to developing fluoroquinolone-induced tendinopathy.

## References

- Sharma A (2014) Therapeutic drug monitoring of gentamicin : A prospective study. *Int J curr pharm & Clin Res* 4: 139-144.
- Schindler C, Pittrow D, Kirch W (2003) Reoccurrence of levofloxacin-induced tendinitis by phenoxymethylpenicillin therapy after 6 months: a rare complication of fluoroquinolone therapy? *Chemotherapy* 49: 90-91.
- Sterne GM, Richardson ML, Warren BH (2006) Imaging findings in two cases of fluoroquinolone-induced achilles tendinopathy. *Radiol Case Rep* 1: 87-91.
- Kim GK, del Rosso JQ (2010) The risk of fluoroquinolone-induced tendinopathy and tendon rupture: What does the clinician need to know? *J Clin Aesthet Dermatol* 3: 49-54.
- Egger AC, Berkowitz MJ (2017) Achilles tendon injuries. *Curr Rev Musculoskelet Med* 10: 72-80.
- Shimatsu K, Subramaniam S, Sim H, Aronowitz P (2014) Ciprofloxacin-induced tendinopathy of the gluteal tendons. *J Gen Intern Med* 29: 1559-1562.
- Gold L, Igra H (2003) Levofloxacin-induced tendon rupture: a case report and review of the literature. *J Am Board Fam Pract* 16: 458-460.
- Sharma A, Baldi A, Sharma DK (2017) Drug-induced generalized skin eruption in a diabetes mellitus patient receiving a metformin plus simvastatin in a tertiary care teaching hospital in Punjab. *Curr Res Diabetes Obes J* 4.
- Kushawaha SK, Sharma A, Ralta A, Sharma R, Raj D (2014) Pharmacovigilance study : Drugs used in the treatment of tuberculosis at civil hospital Rohru (Shimla), Himachal Pradesh. *Int J Adv Case Reports* 1: 38-42.
- Mahabadi VP, Nasiripour S, Farasatinasab M, Nadjafi S (2017) A case of ciprofloxacin-associated achilles tendinitis. *Physiol Pharmacol* 21: 172-174.
- Ham P, Maughan KL (2016) Achilles tendinopathy and tendon rupture. *Up To Date* 6: 1-6.
- Tanne JH (2008) FDA adds "black box" warning label to fluoroquinolone antibiotics. *BMJ* 337: a816.
- The Food and Drug Administration. [http://www.fda.gov/Drugs/Drug Safety/Post market Drug Safety Information for Patients and Providers/ucm126085.htm](http://www.fda.gov/Drugs/Drug%20Safety/Post%20market%20Drug%20Safety%20Information%20for%20Patients%20and%20Providers/ucm126085.htm) (accessed 2011Jun 23).
- Zwiers R, Wiegerinck JI, van Dijk CN (2016) Treatment of midportion Achilles tendinopathy: an evidence-based overview. *Knee Surgery, Sport Traumatol Arthrosc* 24: 2103-2111.
- Maffulli N, Oliva F (2010) Achilles Tendinopathy. *Eur Instr Lect* 10: 191-199.
- Ganske CM, Horning KK (2012) Levofloxacin-induced tendinopathy of the hip. *Ann Pharmacother* 46.
- Hu CT, Flemister AS (2008) Insertional achilles tendinopathy: surgical options. *Oper Tech Orthop* 18: 247-253.
- Alfredson H, Cook J (2007) A treatment algorithm for managing Achilles tendinopathy: new treatment options. *Br J Sports Med* 41: 211-216.
- Sendzik J, Shakibaei M, Schäfer-Korting M, Stahlmann R (2005) Fluoroquinolones cause changes in extracellular matrix, signalling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. *Toxicology* 212: 24-36.
- Thacker SB, Stroup DF, Branche CM, Gilchrist J, Goodman RA, et al. (2003) Prevention of knee injuries in sports: A systematic review of the literature. *J Sports Med Phys Fitness* 43: 165-179.
- Knobloch K, Kraemer R, Jagodzinski M, Zeichen J, Meller R, et al. (2007) Eccentric training decreases paratendon capillary blood flow and preserves paratendon oxygen saturation in chronic achilles tendinopathy. *J Orthop Sport Phys Ther* 37: 269-276.
- Knobloch K, Kraemer R, Lichtenberg A, Jagodzinski M, Gossling T, et al. (2006) Achilles tendon and paratendon microcirculation in midportion and insertional tendinopathy in athletes. *Am J Sports Med* 34: 92-97.
- Lewis T, Cook J (2014) Fluoroquinolones and tendinopathy: A guide for athletes and sports clinicians and a systematic review of the literature. *J Athl Train* 49: 422-427.
- Van der Plas A, de Jonge S, de Vos RJ, der Heide HJLV, Verhaar JAN, et al. (2012) A 5-year follow-up study of Alfredson's heel-drop exercise programme in chronic midportion Achilles tendinopathy. *Br J Sports Med* 46: 214-218.

25. Rompe JD, Furla JP, Maffulli N (2008) Mid-portion achilles tendinopathy - Current options for treatment. *Disabil Rehabil* 30: 20-22.
26. Lopez RGL, Jung HG (2015) Achilles tendinosis: Treatment options. *Clin Orthop Surg* 7:1-7.
27. Dey A, Godsiff SP, Pandey R (2004) Acute calcific tendinitis mimicking patella tendon rupture. *Inj Extra* 35:104-107.
28. Nandra RS, Matharu GS, Porter KM (2012) Acute achilles tendon rupture. *Trauma* 14: 67-81.
29. Sharma A, Anghore D, Awasthi R, Raj D (2014) Pharmacovigilance study of hypertensive drugs. *Medicat Guid* 2: 58-69.
30. Sugimoto T, Kaneko H, Deji N, Koya D (2005) Levofloxacin-induced Achilles tendon rupture in a patient with systemic microscopic polyangiitis. *Mod Rheumatol* 15: 217-219.
31. Bailey RR, Kirk JA, Peddie BA (1983) Norfloxacin-induced rheumatic disease. *N Z Med J* 96: 590.