A STUDY OF ASSOCIATION OF FLUOROQUINOLONES IN TENDINITIS AND ASSOCIATED COMPLICATIONS

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ABSTRACT

BACKGROUND

Fluoroquinolones are the quinolone antimicrobials, which are known to have one or more fluorine substitutions. The first generation fluoroquinolones, which was introduced in 1980s have one fluoro substitution. This was very affective in cases of gram-negative bacterias.[1] In the 1990s, compounds with additional fluoro and other substitutions have been developed further extending antimicrobial activity to gram-positive cocci and also anaerobes, which also has higher metabolic stability.[2,3,4] It also has a higher half-life. These are referred to as second generation fluoroquinolones. The first generation fluoroquinolone includes norfloxacin, ciprofloxacin, ofloxacin and pefloxacin. Second generation fluoroquinolone includes levofloxacin, lomefloxacin, sparfloxacin, moxifloxacin, gemifloxacin and prulifloxacin. The present topic of controversy is tendinopathy and tendon rupture induced by fluoroquinolone. There is enough data, which suggest that fluoroquinolones should be used with utmost care in population of patients. That means, not all the patients with gram-negative infections can be given this antibiotic as it has its own side effects. The first one to publish report was that of a fifty-six-year-old patient who had urinary tract infection and was treated with norfloxacin. The patient developed Achilles tendinopathy and the associated rupture was reported in New Zealand in the year 1983. Subsequently, there were many other case reports and case-controlled studies reporting similar findings. Fluoroquinolone are commonly prescribed to treat community-acquired infections involving the respiratory, urogenital and gastrointestinal tracts. Fluoroquinolone concentration is seen on a higher scale in bones and joints when compared to the serum levels. So, it is ideal to treat the bones and joint infections. The cartilage infections is also treated with fluoroquinolone. Achilles tendinitis or rupture is among the most serious side effects associated with fluoroquinolone. This study puts in a sincere effort to understand in depth the tendinitis and rupture complications caused by the drugs, which belong to fluoroquinolones. This study is intended to help the general practitioners and the practicing orthopaedicians to know the depth of the disease and to attend the primary cause of the tendinitis and associated rupture secondary to the use of fluoroquinolones.

MATERIALS AND METHODS

Forty patients were selected who attended the Department of Orthopaedics and complained of tendon pain or tendon rupture. The present study was done in the Department of Orthopaedics, Deccan Medical College, at Hyderabad. Detailed history was taken and the patients were divided into 4 age groups. 20-40 years were taken into group-1; 40-60 years were taken into group-2; 60-80 years were taken into group-3 and >80 years old were taken into group-4. Past history was taken in detail and use of fluoroquinolone drugs were asked. Gender-based statistical analysis was not done as female patients were very low in number. All statistical analysis was done using latest SPSS (2015) Software, California.

RESULTS

In the present study, the mean age of the population that was considered for the study was 61.11 years and the standard deviation was 21.739 years. The study group was divided into four groups. 20-40 years were taken into group-1; 40-60 years were taken into group-2; 60-80 years were taken into group-3 and >80 years old were taken into group-4. Group-1 consisted of 3 patients, group-2 consisted of 4 patients, group-3 consisted of the highest number of patients and consisted of 26 patients and the group-4 consisted of 7 patients. Out of the present patients, 2 patients who belonged to group-2 and group-3 complained of tendon rupture and thus there was a strong association of the tendon ruptures with use of fluoroquinolone drugs. Out of the patients, 4 patients who belonged to group-3 and one patient who belonged to group-4 had tendinitis. Thus, there was a strong association of the tendon ruptures with use of fluoroquinolone drugs.

CONCLUSION

There is a positive significant relation between the tendinitis and tendon rupture complications associated with the use of fluoroquinolones. The study successfully shows the association. In a country like ours where these fluoroquinolone drugs are used very commonly has to check its utilisation in a proper way.

KEYWORDS

Fluoroquinolones, Tendinitis, Complications, Antimicrobial, Fluorine.

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BACKGROUND

Fluoroquinolones are the quinolone antimicrobials, which are known to have one or more fluorine substitutions. The first generation fluoroquinolones, which was introduced in 1980s have one fluoro substitution. This was very effective in cases of gram-negative bacterias.[1] In the 1990s, compounds with additional fluoro and other substitutions have been developed further extending antimicrobial activity to gram-positive cocci and also anaerobes, which also has higher metabolic stability.[2,3,4] It also has a higher half-life. These are referred to as second generation fluoroquinolones. The first generation fluoroquinolone includes norfloxacin, ciprofloxacin, ofloxacin and pefloxacin. Second generation fluoroquinolone includes levofloxacin, lomefloxacin, sparfloxacin, moxifloxacin, gemifloxacin and prulifloxacin. The mechanism of action is the fluoroquinolones inhibit the enzyme bacterial DNA gyrase. It is primarily active in gram-negative bacterium, which is known to nick double-stranded DNA introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The DNA gyrase consists of two A and two B subunits. The A subunit carries out nicking of DNA, B subunit introduces negative super coils and then A subunit reseals the strands. The fluoroquinolones bind to A subunit with high affinity and interfere with its strands cutting and resealing function. In gram-positive bacteria, the major target of fluoroquinolones action is a similar enzyme topoisomerase IV, which nicks and separates daughter DNA strands after DNA replication. Greater affinity for topoisomerase IV may confer higher potency against gram-positive bacteria. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA. In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II, which is known to remove positive supercoils, which has very low affinity for fluoroquinolones, hence, this is known to cause low toxicity to host organisms.

Nowadays, there are also incidences for the resistance seen in increasing number. Because of the unique mechanism of action, plasmid-mediated transferable resistance is less likely. Resistance noted so far is due to chromosomal mutation producing a DNA gyrase or topoisomerase IV with reduced affinity for fluoroquinolones or due to reduced permeability of these drugs across bacterial membranes. In contrast to nalidixic acid, which selects single-step resistant mutants at high frequency, fluoroquinolones-resistant mutants are not easily selected. Therefore, resistance to fluoroquinolones has been slow to develop, however, increased resistance has been reported among salmonella, pseudomonas, staphylococci, gonococci and pneumococci.

The present topic of controversy is tendinopathy and tendon rupture induced by fluoroquinolone. There is enough data, which suggest that fluoroquinolones should be used with utmost care in population of patients.[5] That means not all the patients with gram-negative infections can be given this antibiotic as it has its own side effects. The first one to publish report was that of a fifty-six-year-old patient who had urinary tract infection and was treated with norfloxacin. The patient developed Achilles tendinopathy and the associated rupture was reported in New Zealand in the year 1983.[6] Subsequently, there were many other case reports and case-controlled studies reporting similar findings.[7–9] Fluoroquinolone are commonly prescribed to treat community-acquired infections involving the respiratory, urogenital and gastrointestinal tracts.[10] Fluoroquinolone concentration is seen on a higher scale in bones and joints when compared to the serum levels. So, it is ideal to treat the bones and joint infections.[11] The cartilage infections is also treated with fluoroquinolone. Achilles tendinitis or rupture is among the most serious side effects associated with fluoroquinolone.[12]

Some of the antibiotics, which belong to the group, which belong to the fluoroquinolones like ciprofloxacin is rapidly absorbed orally, but food delays absorption and first pass metabolism occurs. All the fluoroquinolone drugs have good tissue penetrability, good concentration in lungs, sputum, muscle, prostate and phagocytes exceeds that in plasma, but CSF and aqueous levels are lower. It is excreted primarily in urine, both by glomerular filtration and tubular secretion. Urinary and biliary concentrations are ten to fifty folds higher than plasma. Thus, in a country like ours, it is one of the most commonly used by the general practitioners and by far by the common people by themselves.

This study puts in a sincere effort to understand in depth the tendinitis and rupture complications caused by the drugs, which belong to fluoroquinolones. This study is intended to help the general practitioners and the practicing orthopaedicians to know the depth of the disease and to attend the primary cause of the tendinitis and associated rupture secondary to the use of fluoroquinolones.

AIMS AND OBJECTIVES

1. To understand the tendinitis and tendon rupture associated with the use of fluoroquinolones.
2. To understand the other complications of fluoroquinolone.

MATERIALS AND METHODS

Forty patients were selected who attended the Department of Orthopaedics and complained of tendon pain or tendon rupture.

The present study was done in the Department of Orthopaedics, Deccan Medical College, at Hyderabad.

Detailed history was taken and the patients were divided into 4 age groups. 20-40 years were taken into group-1; 40-60 years were taken into group-2; 60-80 years were taken into group-3 and >80 years old were taken into group-4.

Past history was taken in detail and use of fluoroquinolone drugs were asked. Gender-based statistical analysis was not done as female patients were very low in number.

Inclusion Criteria

Only positive use of fluoroquinolone drugs if present in the past history was taken for the study.

Exclusion Criteria

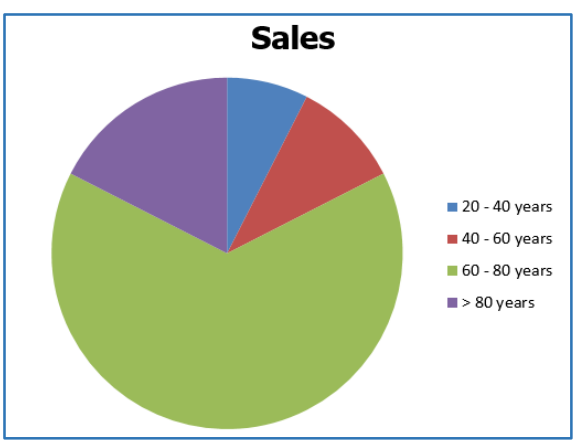
1. Injuries and other trauma cases were not considered.
2. Negative fluoroquinolone drugs usage history was not considered.

All statistical analysis was done using latest SPSS (2015) software, California.

RESULTS

	Mean	Std. Deviation
Age	61.11	21.739

Table 1. Mean Age of the Study Participants (n=40)



Age Distribution

Majority of the patients belonged to the age group of 60-80 years.

	Tendon Rupture		x^2 value	p value
	Present (%)	Absent (%)		
20-40 years	Nil	3	12.988	0.005
40-60 years	1	3		
60-80 years	1	25		
>80 years	Nil	7		
	Tendinitis		X^2 value	p value
	Present (%)	Absent (%)		
20-40 years	Nil	3	8.920	0.030
40-60 years	Nil	4		
60-80 years	4	22		
>80 years	1	6		

Table 2. Association of Tendinitis, Tendon Rupture and Associated Complications

There is a strong significance between tendinitis and tendon rupture and fluoroquinolones usage.

Complications	20-40 Years	40-60 Years	60-80 Years	>80 Years
Gastrointestinal	2	1	6	3
CNS	Nil	1	11	2
Skin hypersensitivity	1	1	5	1

Table 3. Other Commonly-Associated Complications

DISCUSSION

In the present study, the mean age of the population that was considered for the study was 61.11 years and the standard deviation was 21.739 years. The study group was divided into four groups. 20-40 years were taken into group-1; 40-60 years were taken into group-2; 60-80 years were taken into group-3 and >80 years old were taken into group-4. Group-1 consisted of 3 patients, group-2 consisted of 4 patients, group-3 consisted of the highest number of patients 26 patients and the group-4 consisted of 7 patients.

Out of the present patients, 2 patients who belonged to group-2 and group-3 complained of tendon rupture and thus there was a strong association of the tendon ruptures with use of fluoroquinolone drugs. Out of the patients, 4 patients who belonged to group 3 and one patient who belonged to group-4 had tendinitis. Thus, there was a strong association of the tendon ruptures with use of fluoroquinolone drugs.

The present study is in agreement with other studies conducted by Grace K. Kim and Yasmin Khaliq et al.[13-14]

Fluoroquinolones has good safety record. A side effect occurs in about 10% of the patients, but is generally mild. Withdrawal is needed only in about 1.5%. Gastrointestinal side effects include nausea, vomiting, bad taste and anorexia. Because gut anaerobes are not effected diarrhoea is infrequent. CNS disturbances include dizziness, headache, restlessness, anxiety, insomnia, impairment of concentration and dexterity. So, it should be cautiously used while driving. Tremors and seizures will be occasionally seen and is known to occur in high doses or when predisposing factors are present. Possibly, it is reflect GABA antagonistic action of fluoroquinolones. Skin hypersensitivity includes rash, pruritus, photosensitivity, urticaria, swelling of lips, etc. Serious cutaneous reactions are rare.

Because of the broad-spectrum activity of these drugs, it has been rampantly used in this part of the country. The side effects even though are few and rare, but if it sets in may, cause lifelong consequences. So, it is important to check its use and proper law has to be enforced to check its utilisation.

CONCLUSION

There is a positive significant relation between the tendinitis and tendon rupture complications associated with the use of fluoroquinolones. The study successfully shows the association. In a country like ours where these fluoroquinolone drugs are used very commonly has to check its utilisation in a proper way. When such catastrophes occur, it is mandatory to stop the drugs and take immediate steps, so the progression of the disease can be halted.

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