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Toxicological Aspects of Fluoroquinolones Administration: A Literature Review

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Abstract

Fluoroquinolone associated toxicity after along-term fluoroquinolone antibiotic therapy appears as a significant medical and social problem. The objective of this review was mainly to identify, collect and evaluate the available evidence regarding the toxicological aspects of fluoroquinolone with focus on the causes offluoroquinolone chondrotoxicity in juvenile animals.The presentreview was conducted using the PubMed/Medline databases.English language publications, original studies and reviews were included. All works about the fluoroquinolones regarding human, in vitro, and animal studies published in the medical and dental literature between 1985 and 2021 were reviewed.The existing data studies demonstrate that fluoroquinolone administration cancause different side effects, and the fluoroquinolone chondrotoxicity in juvenile animals is one of them. The cause could be due to binding offluoroquinolone with the divalent cations such as Mg2+ and this can induce a deficiency of the functionally available magnesium, increaselevel of tissue apoptotic markers like activated caspase-3, reactive oxygen species (ROS) overproduction, mitochondrial damage, enhanced the expression of matrix metalloproteinases, with chondrocytes loss and decrease in the formation of the cartilage extracellular matrix.Depending on these toxicological findings in animal'sstudies during the postnatal growth,fluoroquinolones are contraindicated during pregnancy, lactation,and in children.

Keywords:Fluoroquinolones, Antibiotics, Chondrotoxicity,Caspase,Mg^{2+}.

1. Introduction

Nalidixic acid, thequinolone, was a byproduct of the synthesis of chloroquine in 1960 "[1]". The spectrum of its activity against the gram-negative bacteria of this non-fluorinated substance is very narrow.Later in the 1980 fluorinated derivatives were synthesized "[2]". The fluorinated analoguesof the nalidixic acid, a 1,8-naphthyridine with a4-quinolone nucleus areimportant compounds of fluoroquinolones (Figure -1). The C-6 carbon of the basic ring structure is the site of fluorination [as comes in1 and 2].They have a broad antibacterial activity that includes both gram negative and positiveaerobic with the anaerobic species "[3, 4]".

The active substances of fluoroquinolones are ciprofloxacin, enoxacin, cinoxacin, levofloxacin, flumequinmoxifloxacin, lomefloxacin, ofloxacin, norfloxacin, pefloxacin, prulifloxacin,rufloxacin and pipemidic acid. They are prescribed widely and are important for the treatmentof aserious bacterial infection"as mentioned in [5]". Ciprofloxacin, which is the most widely and successfully used fluoroquinolones, was marketed in 1986, and since that time, the fluoroquinolones uses for the treatment of different infectious diseases have become so widely increased"as comes in [6]".The fluoroquinolones classification on the basis of their pharmacokinetic and the characteristic features is seen inTable-1"[7,8,9,10]".

Fluoroquinolones act by inhibition of the DNA gyrase bacterial enzyme, which nicks the double-stranded DNA, and produces negative super coils. After that it cause resealing to the nicked end. This action cause prevention in the positive supercoiling of DNA strands when they are separate in order to facilitate replication and transcription. This inhibitory action can interrupt the DNA replication and transcription, and preventing cell division in different bacterial cells [as comes in 5, 11,12].

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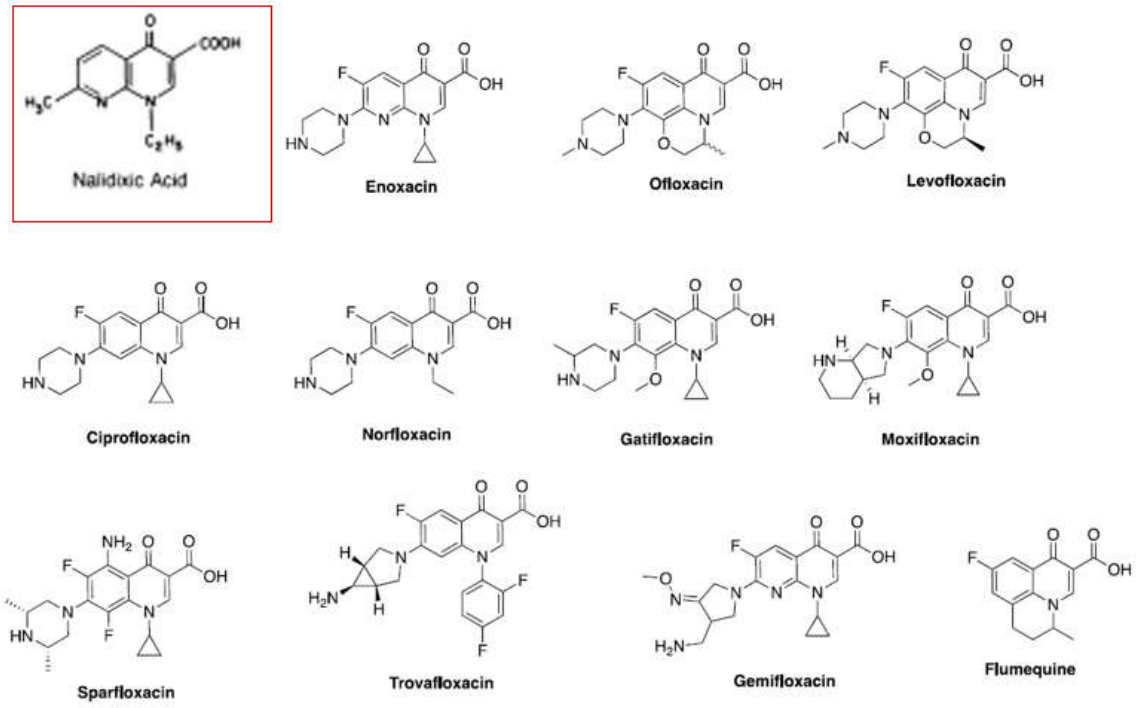

Figure1: Structure of nalidixic acid and some selected fluoroquinolone.

Table 1: Fluoroquinolones classification

Type of generation	Type of drug	Characteristic features
First	Naldixic acid Pipemidic acid Oxolinic acid	Activity against some gram-negative bacteria. High protein binding about 90%. Associated with little half-life. Bacteria can develop a rapid resistance.
Second	Ciprofloxacin Norfloxacin Enoxacin Ofloxacin Lomefloxacin	Activity against gram positive and negative bacteria. Protein binding about 50% with improved tissue distribution. Associated with longer half-life.
Third	Temafloxacin Sparafloxacin Grepafloxacin	Active against the gram positive and the gram-negative bacteria.
Fourth	Clinafloxacin Gatifloxacin Trovafloxacin Moxifloxacin	Active against anaerobes and atypical bacteria. Extended activity against both strains of bacteria.

2. Fluoroquinolone general information

2.1. Antimicrobial properties

Fluoroquinolones havea good and a wide spectrum activity against thegram - positive andgram-negative bacteria, and this activity against the both types was seen associated with some types of them"[7]".Excellent activity wasseen against the gram-negativetype such as the members ofthe family of Enterobacteriaceae, *Haemophilus influenzae, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Moraxellacatarrhalis*, and *Neisseria meningitides.*

Most of gram-negative bacteria are responsible forthe urinary tract infections showed high sensitivityto fluoroquinolones [as comes in 13].

Ofloxacinand ciprofloxacin and were showed excellent activity against the*staphylococcus aureus*, like the penicillin and methicillinsensitive strains. Several other bacteria are inhibited by the fluoroquinolones use like species of *Chlamydia, Legionella, Mycoplasma,Mycobacterium, and Brucella.*Levofloxacin,grepafloxacin, sparfloxacin,and trovafloxacin shows a significantactivity against the*Mycoplasma pneumonia, Chlamydia pneumoniae,*and *Legionella pneumophila.*Ofloxacin and ciprofloxacin shows less activity against the*Mycobacterium tuberculosis*"[14]". Trovafloxacin was seen active against *B. fragilis,Peptostreptococci, Clostridium perfringens,* and *C.difficile*. The fluoroquinolones ability to decrease SARS-CoV-2 replication in vitro was seen very limited "as comes in [15]".

2.2. Development of microbial resistance: The wide use of the fluoroquinolones causes increasing concern for development of microbial resistance. Several mechanisms for development of resistance were seen ["as mentioned in 16 and 17]":

1. Development of genesmutations which encode bacterial topoisomerase II and IV, this result in altered binding affinity of the drug and reduction in its action.
2. Reduction in intracellular drug exposure due to development of bacterial efflux transporters.
3. A plasmid which carries the gene *qnrA*has been discovered which leads to the inherent mechanism of resistance.

2.3. Drug interaction

Absorption of fluoroquinolones by oral administration is drastically decreased by using antacid containing aluminum, magnesium, and sucralfate. The new compounds interact with multivalent cation containing compounds. Decreasein the oral bioavailability can be by ranitidine. This indicates that the oral absorption of some types of fluoroquinolones can be affected by the gastric pH which affects the dissolution "[8]".Interaction between fluoroquinolones and methylxanthines like caffeine was also found, which can increasethe serum theophylline to a great extent "[18]".

Buck (1998) study found that the antineoplastic drugs serum concentration was seen decrease because of the interaction with ciprofloxacin"[19]".Interaction with probenecid, cimetidine, and azlocillin causing decrease in clearanceof these drugs with increased in serum level of ciprofloxacin"as comes in [19,20]". The drugs, like citrates andsodium bicarbonate which causes the urine to be alkaline, cause reduction in the norfloxacin solubility and hence the development of crystalluria "[20]".

2.4. Pharmacokinetic

The pharmacokinetic profile of newer analogs of fluoroquinolones shows a long serum half-life, greater maximum plasma concentration,more extensive coverage above the minimum inhibitory concentration and permits one daily dose [as comes in21]". Fluoroquinolones when are used with other antibiotic classes, like aminoglycosides and beta-lactams, they are not predictably synergistic"[15]". Following oral the administration, the complete absorption of fluoroquinolones is not always achieved "[8]".The peak serum concentrations of most types of the fluoroquinolones are achieved in one to three hours after oral administration"[22]".

After oral administration, most fluoroquinolonesshow little binding to plasma proteins, and for this reason, the distribution of fluoroquinolones to tissues is superior tomost other antibiotics "[as comes in 23]", and ahigh drug level is found in prostate gland,kidney, lung, and liver. Fluoroquinolones are distributed rapidly in tissues"[24]".Only in the brain, the P-glycoprotein can play important role in this condition"[25]".

Most of fluoroquinolones are eliminated by the kidneyby the glomerular filtration and tubular secretion, so the dosage adjustment is important in patients suffered from renal failure. The liver is the secondary route of excretion. Peritoneal dialysis and hem dialysisare poor way for clearing fluoroquinolones "[22]".

2.5. Therapeutic uses

The fluoroquinolones areused widely, and this use is constantly growing. It was used widely for the treatment ofurinary tract infections and prostatitis "[26]", gastrointestinal infections "[27]", typhoid fever"[28]", rectaland/or pharyngeal gonococcal infections "[29]",sexually transmitted disease "[30]", pneumonia"[31]", osteomyelitis "[13]", and mycobacterial diseases, especially tuberculosis and leprosy "[32]".

2.6. Adverse effects

The most common side effects are hypersensitivity"[33]", tendon/articular toxicity "as comes in [34,35,36,37,38]", numbness, seizures, insomnia, restlessness, convulsions, psychosis ["as comes in39,40,41], nausea, vomiting, diarrhea, headache, and insomnia "[42]", cardiotoxicity "[43]", hepatic toxicity"[44,45]", photosensitivity "[16]",

development of type 2 diabetes mellitus "[46]", and rarely renal failure "[47]". For this reason,the fluoroquinolone use was decreased with the largest decreases was found in inpatient,especially the ciprofloxacin users"[48]".

3. Fluoroquinolone chondrotoxicity

During pregnancy, fluoroquinolonesare contraindicated, as well as in lactation period, children and adolescents, depending on the toxicological results in animals'studies during the postnatal growth "[49]". The chondrotoxicity in some animals was induced by some quinolones by a doseof 10mg/kg b.w. Butto induce joint arthropathy in rats ahigher dose is needed"[50]".

3.1 Clinical features

The cartilage lesion was found limited to juvenile animals only, but in case with pefloxacin treatment, thesechanges have been found in adult and juvenile dogs, but after a prolonged administration of the drug"[51]". Clinically,the most common features are joint pain and swelling, and un ability to walk seenwas seen in severe cases"[52]".Bilateralsolitary or multiple protruding blisters are seen associated with the articular cartilage of the epiphyses of bones. Some articular cartilages were seen associated with erosion of the upper surface. The articular cartilage lesions show a tendency toword healing even in case of a continued adminstration of the fluoroquinolone, but this healing is incomplete even after a long recovery period "[53]".

3.2. Magnetic resonance image

Magnetic resonance image of the joints showed a thickened articular cartilage with surface irregularities. Due to synovial effusion, separation of the opposing articular surfaces was also seen"[54]".

3.3. Histological features

The histological changes which are usually detected are:Degeneration and necrosis of the chondrocyte's cells, matrix degeneration with marked decrease in stainability with Safranin O, cavitation or cleft formation inthe center of edematous articular cartilage which may be detached and lead to the formation of erosions, loss of proteoglycans, alters collagen fibrillogenesis"as comes in [55,56,57,58]".

3.4. Causes

The possible explanation of fluoroquinolone chondrotoxicity could be due to:

3.4.1.Chelating properties of fluoroquinolones against the metal ions

Fluoroquinolones have two sites for formation of metal chelate; the carboxyl and the carbonylgroups which represent the mostimportant coordinate mode in the chelation. They can bind the divalent tor the trivalent cations such as Mg2+, Ca2+, Cu2+, Zn2+, Fe2+, Co2+,A13+ and Fe3+"[59]". A deficiency of functionally available magnesium was induced because of the formation of a chelate complexes with divalent cations like Mg 2+"[60]". It was found that the activity of integrin receptors of the β1 subfamily which can activate the chondrocyte interaction with fibronectin, type I and type II collagen and also important in cell-matrix interactions in the cartilage of the jointis strongly depend on extracellular concentrations of magnesium "as comes in [61,62,63]".

By electron microscopy, it was found that the effects of one dose of ofloxacin can cause the sameeffects in cartilage of animals with aMg2+deficient diet. The arthropathy induced by fluoroquinolones may beat tribute to thedecrease of the functionally available Mg2+ in thecartilage of the joint"[64]". The supplementation of Mg2+ accompanying with the fluoroquinolone's treatment can decrease the cartilage lesions "[65]". In immature dogs, the Mg2+ deficient diet can inducethe similar clinical features as quinolones. Alterations in fibronectin staining and other extracellularstructures were seen"[66]". This explains that the addition of Mg2+ can restores the extracellular Mg2+dependent inter cell interactions in condylar cartilage.

Iron chelation can mediatethe epigenetic changes. The dioxygenase (HIF -1α) mRNA translation inhibition, and the repression of prolyl 4-hydroxylase (P4HA1) and lysyl hydroxylase (LH1) transcription,may be result also intoxicity "as mentioned by [60,67,68]". Fluoroquinolones is a potent iron chelator like deferoxamine, and this iron chelation resulted in suppression of collagen prolyl hydroxylation as well as DNA and histone hypermethylation"[69]".

3.4.2. Induced apoptosis

Apoptosis plays a role in fluoroquinolone induced arthropathy [70].It was demonstrated that, after therapeutic uses of fluoroquinolones like ciprofloxacin and levofloxacin,the tissue levels of the apoptotic markers like activated caspase-3 was increased"[49]". Apoptosis was seen even at the lowest concentration, and confirmed by electron microscopy. The condensed materials in the nucleus and apoptotic bodies can be caused after fluoroquinolones treatment "[49]". Liu*et al* (2015) also found that enrofloxacin can cause increase in the malondialdehyde concentration, and induced cell apoptosis"[71]".

3.4.3. Increase oxidative stress (ROS overproduction)

Many studies explained that quinolones can cause cell damage due to the induced increase the ROS. Mitochondrial DNA damage can result from the overproduction of ROS, this overproduction cantriggerapoptosis bythe releasing of the caspase activating markers and causing damage of tissue "[72]". Extracellular matrix components can also affect by ROS by direct cytotoxic effect, by oxidizing collagen's amino acids andby protein conformation changes, and increase in the matrix metalloproteinases,which cause a synergistical increase in the toxicity [as it was concluded by 73].

3.4.4. Mitochondrial damage

During quinolones treatment, the mitochondrial damage can be seen in cartilage, bone and tendon"as comes in [74,75,76]". The inhibition of the mitochondrial electron transport chain complexes activity after fluoroquinolones treatment can cause mitochondrial respiration inhibition with reduction ofthe ATP production"[77]".The mitochondria are important target by the oxidative stress, so the ROS overproductioncancause a severe oxidative damage to the mtDNA in cartilage cells"[78]". Cytochromec which can be released by mitochondriacauses the start of the signaling pathway and later leads to activation of caspases which causes the apoptosis and the development of tissue lesions"[79]".

3.4.5. Enhancethe expression of matrix metalloproteinases

Thematrix metalloproteinase are enzymeswhich play a role in response to tissue injury and in homeostasis"[72]". Studies in animals found that the fluoroquinolones can enhance the activity of matrix metalloproteinases at the mRNA in cells andaffect type I collagen metabolism causing collagen degradation "as comes in [80]".

3.4.6. Chondrocytes loss and decrease in the formation of the cartilage extracellular matrix

It was found that fluoroquinolone treatment can significantly decrease the number of chondrocytes and the thickness of condylar cartilage with a mark decrease in collagen synthesis. The glycosaminoglycan content of the articular matrix was found to be decreased after its administration due to inhibition of DNA synthesis and inhibitory action of quinolones on proteoglycan synthesis in the chondrocytes"[81]".

4. Fluoroquinolone contraindications

The use of fluoroquinolones is contraindicated in patients with: Hypersensitivity "[33,82]", epilepsy or psychotic disorder, neuropathy, or with a known predisposition to seizures [83,84], tendon disorders related to fluoroquinolone administration, especially in patients with current or past treatment with oral corticosteroids"as comes in [35,85,86]", impaired renal function since they are eliminated mainly via the kidneys "[47]", and children because of the risk of musculoskeletal injury "[87]".

Because it is excreted into human breast milk and can cause arthropathy, breast-feeding should be discontinued. After two hours, the milk concentration was highest with 3.79 mg/L and it then decreased to 0.02 mg/L afterone day"[88]".Fluoroquinolones must be used with caution in patients with liver diseases"[89]", cardiac diseases "[90]", myasthenia gravis"[91]", disturbances in blood glucose level "[92]", and patients treated with vitamin K antagonists "[93]".

5. Conclusion

Existing data from different studies consistentlydemonstratethat fluoroquinolones administrations are seen associated several side effects, and thefluoroquinolones chondrotoxicity is one of the important adverse effects. For this reason, fluoroquinolonesare contraindicated during pregnancy, lactation period, inchildren and even adolescents. The possible explanation of fluoroquinolone chondrotoxicity in juvenile animals could be due to:Chelating properties against the metal ions like Mg +2, increase in the tissue levels of the apoptotic markers like activated caspase-3, oxidative stress overproduction, mitochondrial damage in condylar cartilage, enhance the enzymatic activity of matrix metalloproteinases in cells, chondrocytes loss and decrease in the formation of the cartilage extracellular matrix.

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النواحى السميه لاستخدام الفلوروكينولون مراجعه مقالات

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الخلاصه
تظهر السمية المرتبطة بالفلوروكينولون بعد العلاج طويل الأمد بالمضادات الحيوية بالفلوروكينولون كمشكلة طبية واجتماعية كبيرة. كان الهدف من هذه المراجعة بشكل أساسي هو تحديد وجمع وتقييم البَيِّنَة المتاحة فيما يتعلق بالجوانب السمية للفلوروكينولون مع التركيز على أسباب السمية الغضروفية بالفلوروكينولون في الحيوانات اليافعة. أجريت المراجعة الحالية باستخدام قواعد بيانات PubMed / Medline. تم تضمين المنشورات باللغة الإنجليزية والدراسات الأصلية والمراجعات. تمت مراجعة جميع الأعمال المتعلقة بالفلوروكينولونات المتعلقة بالدراسات البشرية والمختبرية والحيوانية المنشورة في الأدبيات الطبية وطب الأسنان بين عامي 1985 و 2021. تظهر دراسات البيانات الحالية أن إعطاء الفلوروكينولون يمكن أن يسبب آثارًا جانبية مختلفة ، والسمية الغضروفية الفلوروكينولون في الحيوانات الصغيرة هي واحدة منها. قد يكون السبب هو ارتباط الفلوروكينولون بالكاتيونات ثنائية التكافؤ مثل Mg+2 ويمكن أن يؤدي ذلك إلى نقص المغنيسيوم المتاح وظيفيًا ، وزيادة مستوى علامات موت الخلايا المبرمج في الأنسجة مثل كاسباس المنشط - 3 ، والإفراط في إنتاج أنواع الأكسجين التفاعلية (ROS) ، وتلف المايتوكوندريا ، وعزز التعبير عن الماتريكس ميتالوبوتينيسس. اعتمادًا على هذه النتائج السمية في الدراسات التي أجريت على الحيوانات أثناء النمو بعد الولادة ، يتم منع استخدام الفلوروكينولونات أثناء الحمل والرضاعة وعند الأطفال