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Ciprofloxacin Chemistry, Medical Evaluation and Adverse Effect with Special Attention to Ciprofloxacin Chondrotoxicity

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Abstract

Ciprofloxacin is the most potent fluoroquinolone and was seen active against a broad range of bacteria. The present study was aimed to review all published animals and human studies in the medical and dental literature about ciprofloxacin use in the period between 1995 and 2021. English language publications, original studies and reviews were included.Several researchers revealed that ciprofloxacin can causes arthropathy. Chondrotoxicity seen in juvenile animals could be due to the deficiency of functionally available magnesium, production of oxidative stresses and lipid peroxidation, chondrocytes loss, decrease in the formation of the cartilage extracellular matrix, decrease in sox9 expression, increase caspase-3 and matrix metalloproteinases expression.In human, ciprofloxacin can induce tendinopathy and tendon rapture. Follow up of children which were treated with ciprofloxacin, showed that only a few percentages of them had developed a ciprofloxacin-related acute arthropathy, but it cannot cause any permanent joint damage. The majority of events were mild to moderate severity. These researches indicatedthat ciprofloxacin may be a safe drug to be used in children under the age of 18 years old, but only used when there is no a good alternative to its use until a long-term follow-up studies are completed.

Keywords: Ciprofloxacin, Arthropathy, Chondrotoxicity, Fluoroquinolone

1. Introduction

The nalidixic acid was the synthesis byproduct of the chloroquine in 1960. It is effective primarily against gram-negative bacteria, with minor anti-gram-positive activity and showed unfavorable pharmacokinetic properties. Later in the 1980, the fluorinated derivatives were synthesized, which possess a broad antibacterial spectrum that includes the gram negative and the gram positive aerobic with the anaerobic species"[1]". One of the most widely used and successful compounds of the fluoroquinolone, is ciprofloxacin, which was first patented by Bayer AG in 1983 and then approved by United States FDA (Food and Drug Administration) for use in the year of 1987. It is considered as the second generation of the quinolones and considered as a broad-spectrum antibiotic and the most potent fluoroquinolone "as comes in [1 and 2]".

Chemistry of ciprofloxacin

Ciprofloxacin hydrochloride is a monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-1-piperazinyl-3-quinolinecarboxylic acid, and yellowish crystalline substance. Ciprofloxacin formula is C17H18FN3O3 with a molecular weight is 331.4. A number of ciprofloxacin derivatives are also present which showed improved potency. Nalidixic acid and ciprofloxacin chemical structures are as seen in Figure 1[as mentioned in 2]:

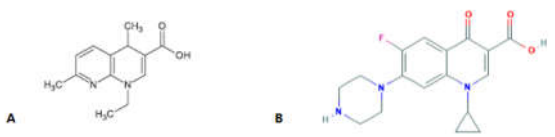

Figure 1: (A) Nalidixic acid. (B) The chemical structure of ciprofloxacin

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Mechanisms of action of ciprofloxacin

Inside bacterial cells, ciprofloxacin has target to the DNA gyrase enzyme (type II topoisomerase). A negative super helical twist into bacterial DNA was introduced by which is essential enzyme in DNA replication. By inhibiting DNA gyrase enzyme, ciprofloxacin inhibits the DNA synthesis. The second target for the ciprofloxacin is topoisomerase IV which carries out the relaxation of DNA, and thus helps in the segregation of the replicating chromosomes. Inhibition of topoisomerase IV is important factor which contributing to the bactericidal activity of the ciprofloxacin. This inhibitory action can interrupt the DNA replication and preventing the cell division in bacterial cells "as discussed by [3, and 4]".

Reasons for ciprofloxacin use

The reasons for ciprofloxacin widely use are susceptibility of the multi-resistant pathogens only to ciprofloxacin treatment, higher plasma concentrations, greater bioavailability, and increased tissue penetration. Its minimum inhibitory concentration is more superior to any other fluoroquinoloneswhen examined against several types of gram-negative or gram-positive bacteria, and the oral ciprofloxacin is superior to ampicillin for the treatment typhoid fever [2].
Ciprofloxacin had also showed a significant interest because of its apoptotic and antiproliferative activities in different cell lines of cancer. It causes apoptosis and inhibition growth of various carcinoma, leukemiacell lines, and osteosarcoma. It was found that a doses of 50-400 µg/ml ciprofloxacin, which is used currently for treatment of different types of bacterial infections, can inhibited the bladder cancer cell growth, activated the apoptotic processes and causes the S/G2M cell cycle arrest [as carried out by 5].

Clinical indications for ciprofloxacin

Ciprofloxacin is important antibiotics which is commonly used for: urinary, intestinal, and respiratory infections, which is caused by a different types of microorganisms like N. meningitides, Hemophilus influenzae, Escherichia coli, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila, Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus pneumoniae, Enterococcus faecalis, Moraxella catarrhalis, Staphylococcus epidermidis, in addition to Streptococcus pyogenes[6].

Ciprofloxacin is also showed effectiveness against a broad spectrum of infectious diseases including those which are difficult to treat. Oral ciprofloxacin or intravenous injections are used for treatment of bone infections "[7]", febrile neutropenia, and anthrax "[8]", gastrointestinal infections "[9]", lower respiratory tract infections and pneumonia "[10]", chronic bacterial prostatitis and urinary tract infection "[11]", and complicated pyelonephritis in pediatrics "[12]". Various quinolone derivatives have been screened for their antifungal activities, and was seen exhibited potency against fungi"[13]". But they exhibit a low antiviral activity against SARS-CoV-2 and MERS-CoV "[14]".

Administration

For the treatment of mild to moderate infection, the recommended oral dose regimen of ciprofloxacin is 250 mg two times daily, or 500 mg two times daily for severe urinary tract infections. Complicated infections need a higher dosage of 750mg twice daily. It is better to take ciprofloxacin medicine on an empty stomach to works best, and it is recommended to avoid giving antacids, dairy products such as milk and yogurt, iron, and Zinc supplements within four hours of the dose"as mentioned by [15]".

The intravenous dosage of 200 to 400 mg of ciprofloxacin two times daily is indicated for the treatment of moderate or mild infections, but 400 mg three times daily is used for a life-threatening infection. It must be given intravenously by slow infusion over 60 minutes. The topical type is safe and indicated for the treatment of otitis media "[2]".

The use of quinolones during the first months of pregnancy is not seen associated with the risk of premature births or birth defects. But other studies are needed to evaluate the side effects of ciprofloxacin in the developing fetuses.The different types of ciprofloxacin are approved by the FDA (2012) to be used in children only in cases with anthrax and severe urinary infections or in pyelonephritis, but never as first-line agents because of the risk of damage to the musculoskeletal system. Ciprofloxacin is considered as a first-line for treatment of dysentery in the WHO Pocket Book of Hospital Care for Children "[16]", with oral dose of 10-15 mg/kg two times daily for five days, but they recommended that its use in children is only when the benefits outweigh the risk of arthropathy"as explained by[17]".

Pharmacokinetic
Absorption

Ciprofloxacin is readily absorbed following oral administration, but this absorption is not complete. The absolute bioavailability is within a range of 70–80% for the oral dose. The intravenous infusion of 400 mg given over 60 minutes twice daily has shown to produce a serum concentration the same like that which is produced by oral dose of 500 mg given twice daily "[2]".The concentrations of ciprofloxacin in the interstitial fluid space, were lower than the corresponding that in the plasma after a dosage of 400 and 500 mg. After intravenous injection of 200 mg ciprofloxacin, the concentration in the tissue of brain was 0.87 ± 0.08 mg/kg, this suggested that a greater dose of ciprofloxacin is needed to ensure the therapeutic level needed in tissue of the brain. The cerebrospinal fluid concentration was also considered to be subtherapeutic, this is because of the slow flux of ciprofloxacin across the blood–brain barrier "[18]".

Distribution
Ciprofloxacin showed a little binding to the plasma proteins, for this reason, ciprofloxacin distribution in different types of tissues was seen superior to many other types of fluoroquinolone. The drug concentration in the liver, prostate, kidney, and lung is remarkable. The ciprofloxacin urinary concentration is more than the minimum inhibitory concentration, for this reason, it is mainly indicated for treatment of the urinary tract infections. A small part of ciprofloxacin can pass from the pregnant mother to the fetus due to the presence of a barrier for the transport present in the placenta of the human "[19]".

Elimination
The glomerulus filtration and tubular secretion are important route for elimination, and the liver is the secondary route of excretion. Ciprofloxacin showed poor clearance by the hemodialysis and peritoneal dialysis "[2]".
Bacterial resistance

The important common causes of a clinically significant resistance are the mutation of gyrase with the topoisomerase IV; this causes a weakening in the interactions present between ciprofloxacin and the enzymes of bacteria. The bacteria can also acquire resistance to ciprofloxacin by the plasmid mediated resistance. The bacteria acquire plasmid genes which is important for protecting bacterial enzymes from the action of ciprofloxacin. The -chromosome mediated resistance can also decrease the concentration of the drug within the cells "[20]".It was seen that ciprofloxacin resistance was different from country to another. The causes are the misuse or overuse of ciprofloxacin which can promote the bacterial resistance and limit the ciprofloxacin effectiveness. Uses of prescription drugs without any medical advice or the frequent use of the drugs has also caused the increase in the resistance of bacteria. It was found that the ciprofloxacin formulations numbers that had a concentration which is sufficiently lower than that needed, can leading to increase of the bacteria resistance. The use of more than one prescription of fluoroquinolones to treat a single infection, was seen also associated with increase resistance to ciprofloxacin "as concluded by [20, and 21]".

Drug interactions

The presence of antacids containing aluminum, magnesium, and other agents such as sucralfate causes a decrease in the absorption of oral ciprofloxacin. The multivalent cation containing compounds can also interacts with ciprofloxacin. It may form a stable compound with different metal ions like Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Fe^{2+}, $A1^{3+}$ and Fe^{3+}. Oral ciprofloxacin studies found alterations in its absorption pharmacokinetic parameters when administered simultaneously with magnesium, calcium, aluminum, ferrous, sucralfate, or multivitamins with minerals "[21]".It was also found that zinc can decrease the strength of ciprofloxacin resistance in a laboratory condition. Zinc can decrease the growth of *Escherichia coli* strain. When ciprofloxacin present in combination with zinc, the zinc can retain its inhibitory action, but the ciprofloxacin inhibition of the susceptible types of strain was decreased "[22]".A severe interaction seen occur between ciprofloxacin and theophylline, and antineoplastic drugs with ciprofloxacin. An increased in serum concentration was also seen by interaction with azlocillin, cimetidine, and probenecid "[23]".

Adverse effects

Toxicity of ciprofloxacin is mild at therapeutic dose, in general, vomiting, nausea, hepatotoxicity, diarrhea "[24]", skin photosensitivity, central nervous system complications like dizziness, insomnia, mood alterations, seizures or hallucination and nephrotoxicity "[25]" were reported. It may cause exacerbation of myasthenia gravis "[26]" andhypersensitivity reactions to ciprofloxacin. may also occur "[27]". The Drug-induced bullous pemphigoid has been also reported to be an autoimmune bullous disease induced by ciprofloxacin "[28]".It was found that the use of quinolones is

restricted because of their toxic effects on articular cartilage"[29]". The quinolone uses in children revealed several cases of arthropathy, and the most majority of the patients were used ciprofloxacin.Several reported cases were seen regarding the ciprofloxacin induced chondrotoxicity, tendinopathy"as depicted by [30, and 31]" and tendon rupture both in animals and humans' studies "[32, and 33]" were seen. Like all other fluoroquinolones, ciprofloxacin may damage the weight-bearing joints and contraindicated in children and adolescents in growth phase "[34]".

Chondrotoxicity of ciprofloxacin

Animals' studies

Quinolone-induced arthropathy has been described in different juvenile animals. Regarding ciprofloxacin chondrotoxicity in animals' studies, Table 1 shows a summary of all animal's studies which used ciprofloxacin regarding: Dose and duration of taking ciprofloxacin, age and type of animals, and the concluded results.

Table 1: Details of ciprofloxacin chondrotoxicity in previous animals' studies

Reference	Dose and duration of ciprofloxacin intake	Animal Type	Results
Stahlmann, *et al*, 2000 [35]	Oral dose of 30 and 200 mg/kg for five days	Immature dogs	Cleft and erosions in joint cartilage were seen from 2-5 dogs treated by 200 mg/kg.
Mohansundaram&Mohansundaram, 2001 [36]	Intraperitoneal of 80mg/kg for 15,30, and 45 days.	Juvenile rats	Elevation of serum alkaline phosphatase. Histopathological changes were minimal, moderate and severe according to the dose.
Von Keutz*et al*., 2004[37]	Oral doses of 10,30 and 90 mg/ kg for 14 days	Immature dogs	Only the doses of 30 and 90 mg/kg were seen induced the characteristic arthropathy, and the lesions persisted while the animals were growing.
Li *et al*., 2004 [38]	Intra gastric gavage of 400, 800, and 1200 mg/kg for 7 days.	Juvenile rats	The dose of 800 or 1200 mg/kg were seen causes a matrix degradation, death of chondrocytes with decrease in the cartilage thickness.
Pfister *et al*., 2007 [39]	Subcutaneously injected by 2x600 mg/ kg for one day	Juvenile rats	Induction of cartilage lesion in 92% of rats, the proliferation of chondrocytes and secretion of s proteoglycans seen inhibited.
Channa *et al*. 2008[30]	Intraperitoneal injection of 20 mg/ kg twice daily from 1 - 14 day after birth.	Newly born rat	Retardation of growth plate by inhibiting mitosis, and affected the length of humora and femora.
Maślanka*et al.,* 2009[29]	Oral dose of a single or 5 doses of 10, 50, 100, 300 and 600 mg/kg/day of enrofloxacin (which is metabolized to ciprofloxacin in the body)	21day old male broiler chickens	Single dose of 300 and 600 mg/kg, and 5 days dose with 50, 100, 300 or 600 mg/kg/day can only cause significantly increase in cartilage damage score.
Halawa, 2010 [31]	Oral dose of 20 mg/ kg for 15 days.	Juvenile rats	Induced articular damage, cavity formation and decrease in both articular and epiphyseal growth plate.
Shalaby*et al*, 2015[40]	Intra gastric gavage of 20 mg/kg for 14 days.	Juvenile rats 2 and 5 weeks	Condylar cartilage was affected by erosion of the superficial zone only in pups aged 2weeks. All zones were affected in rats aged 5weeks.
Khazaeel*et al*, 2015 [41]	Subcutaneous of 5mg/kg/day or 35 mg/kg/day enrofloxacin for 15 days	2-month-old male lambs	Decreases of proteoglycans, collagen-II, and in Sox9 expression in both groups. But the caspase -3 expressions showed significant increase in second group only ($P \leq 0.0001$).

Human' studies

In human, ciprofloxacin can induce tendinopathy and tendon rapture. Karande and Kshirsagar [42] follow up the children which were treated with ciprofloxacin, and found that only seven had developed a ciprofloxacin-related acute arthropathy. They concluded that ciprofloxacin use can cause an acute reversible arthropathy, but cannot cause a delayed arthropathy or any permanent joint damage. "Hampel *et al.* [43]"was reported that 10.9% of children receiving 8 mg/kg/day oral ciprofloxacin showed arthropathy compared with 18.9% among 25mg/kg/day intravenous recipients. the majority of events were of mild to moderate severity and resolved without intervention.

A survey during the period 1998-2000 on 525 pediatric patients found that the relative risk of tendon and joint disorder with ciprofloxacin was 1.04% " as concluded by [44]" Two hundred and nineteen treated children with ciprofloxacin were

investigated for the presence of arthropathy "[45]". The study was observed arthropathy in 0.9% of the children, and all the drug related complications were seen reversible, except only one child with arthropathy. "Kaguelidou*et al*. [46]" evaluate the safety, and pharmacokinetics of ciprofloxacin in neonates performed through a systematic literature search from the period 1966 to 2009 and found that when ciprofloxacin was used in neonates after first-line antibiotic therapy, no serious adverse events were seen on cartilage and growth. "Adefurin*et al*. [47]"studied 105 published articles and found that in a total of 16 184 pediatric patients which were taken ciprofloxacin; 258 musculoskeletal side effects were seen, and 50% of the cases were associated with arthralgia and 19% from tendon disorders.

"Masoumi*et al*. [48]" collected data from clinical trials published between 1990 and 2018. Among 16155 pediatric study patients, there were 82 reports of musculoskeletal adverse effects. All these studies indicate a relatively low and reversible risk of arthropathy associated with ciprofloxacin and showed that the musculoskeletal events were reversible after cessation of antibiotics.

Causes of chondrotoxicity

The ciprofloxacin chondrotoxicity is a multifactorial event, and the mechanisms which were reported include:

Deficiency of functionally available magnesium

Some researchers attributed ciprofloxacin articular damage to formation of a chelate complexes, which can induce a deficiency of the available magnesium which result in formation of free radicals. It was found that the condylar cartilage lesions induced by quinolone or by feeding with a magnesium-deficient diet in juvenile rats were identical in histological features, and the administration of magnesium can decrease the induced condylar cartilage lesions which were induced by ciprofloxacin in juvenile Wister rats [39].

Production of oxidative stresses and lipid peroxidation

Some researches attributed the condylar damage in growing animals to the oxidative stress "[38]". Ciprofloxacin was reported to enhance production of the apoptogenic IL-1. Bailly *et al*. [49]found that ciprofloxacin treatment can only increases the ability of human monocytes from peripheral blood for production of TNF- α, IL-1,and IL-6, and after the end of the treatment levels returned to normal level.

IL-1Ɓ, TNF- α, and IL-6 can promote the imbalance between the cartilage destruction and repair by induction of reactive oxygen species (ROS) with different types of inflammatory mediators. ROS can lead to damage to DNA, protein, and lipids. The increase in chondrocytes oxidative activity play important role in matrix degradation. IL-1β can strongly stimulates the cartilage degradation, and also inhibits the proteoglycan and collagen synthesis in condylar cartilage, can increases the production of a proteolytic enzymes like iNOS, COX2 and different cytokines like IL-6 and IL-8, with the production of PGE_2 by chondrocytes, and can reduce the aggrecans production by chondrocytes cells "[50]".

Chondrocytes loss

It was found that ciprofloxacin can significantly decrease the number of chondrocytes and the thickness of condylar cartilage. Halawa [31]study found that ciprofloxacin can decrease the number of chondrocytes in a femoral condylar cartilage, and statistical analysis showed a highly significant decrease in the number of chondrocytes in ciprofloxacin-treated group (75±3.4) compared to (89±1.6) in the control group. The ciprofloxacin-treated group also revealed a significant decrease in thickness of femoral condylar cartilage as compared to control (212.2±1.5 compared to 216.2±1.8μm).

Mitochondria is cell organelles that can produce energy for the cellular function. It requires the topoisomerase enzymes for its maintenance. Ciprofloxacin can inhibit the bacterial topoisomerase gyrase, inhibit the topoisomerase II of our cells, and impairs mitochondrial DNA replication by the inhibition of Topoisomerase II "as described by [3]".

Decrease in the formation of the cartilage extracellular matrix

Aggrecan and collagen and are important structural components of the condylar cartilage, and their degradation was seen associated with progression of the lesion. "Lan *et al*. [51]" study explored the changes of expression of collagen II on fetal articular cartilage of eight pregnant women treated with ciprofloxacin undergoing termination between 19 to 34 weeks, and compared with that of normal fetal cartilage. Results of the study showed that in the normal group, the collagen II was homogeneously distributed in the matrix of articular cartilage, while in the ciprofloxacin group, a markedly decreased staining of collagen II was found in the cartilage, and these changes were results of cartilage lesions. "Williams *et al.* [52]"studied the effect of ciprofloxacin on fibroblast metabolism in vitro, and found that ciprofloxacin caused a statistically significant 36% to 48% decrease in collagen synthesis compared with controls in all fibroblast cultures. Type I collagen was also seen degraded after ciprofloxacin treatment "[53]".

The glycosaminoglycan content of the articular matrix was found to be decreased after ciprofloxacin administration. The femoral epiphyseal growth plate cartilage in "Halawa [31]" study showed decreased staining affinity of the matrix of proliferative zone

and around chondrocyte columns. "Li *et al.* [38]" studies also referred to the reduction in staining intensity and to the decreased synthesis due to inhibition of DNA synthesis and inhibitory action of quinolones on proteoglycan synthesis in the chondrocytes.

Decrease sox9 expression and increase caspase-3 and matrix metalloproteinases expression

It was found that the Sox9 is important for cartilage formation, and regulates the synthesis of matrix components after birth. Apoptosis was playing a role in fluoroquinolone – induced arthropathy and considered as a final event in the pathogenesis of fluoroquinolone induced tendinopathy. A group of cysteine proteases denoted caspases and play a central role in apoptosis, and caspase-3 is one of the most important caspases "[43]".

Articular cartilage of the distal femoral and proximal tibial extremities was investigated by "Khazaeel*et al*. [41]" in lambs given enrofloxacin, which is one of fluoroquinolones that is metabolized to ciprofloxacin in body as active metabolite. The study revealed that sox9 expression can significantly decreased and the caspase-3 expression can significantly increase in the study groups when compared with the control one ($P \leq 0.0001$).

The matrix metalloproteinases (MMPs) role in extracellular matrix degradation has been well investigated, like the MMP-13 was seen plays a significant role in degrading collagen type II "[54]". An increase of MMPs was showed after fluoroquinolone administration in a tendon. Rengel*et al*. [55] found that MMPs especially MMP-3 and MMP-13 were well known responsible for cartilaginous extracellular matrix degradation. Ciprofloxacin can increase the expression levels of MMP-3, MMP-1 [56]and MMP-2 which causes a degradation of collagen type I "[53]".

Conclusion

- ✓ Ciprofloxacin, widely used and successful compounds of the fluoroquinolone, is active against a broad range of bacteria and considered as the most potent fluoroquinolone, and is not recommended for routine use in children.
- ✓ In juvenile animals its use can leads to an arthropathy with irreversible erosion of the joint cartilage.
- ✓ The causes could be deficiency of functionally available magnesium, production of oxidative stresses and lipid peroxidation, chondrocytes loss, decrease in the formation of the cartilage extracellular matrix, and decrease in sox9 expression, increase caspase-3 and matrix metalloproteinases expression.
- ✓ Human studies found that ciprofloxacin can induce tendinopathy, tendon rapture, and reversible arthropathy, but cannot cause any permanent joint damage.
- ✓ It is recommending a cautious during the use of ciprofloxacin in children till a long-term follow-up studies are completed about its use.

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كيمياءالسبروفلوكسازين' التقييم الطبى واثاره السلبيه مع تركيز خاص على سبروفلوكسازين سميه الغضروف

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الخلاصه

السبروفلوكسازين هو اكثر فلوروكينولون قوه وشوهد بانه نشطا ضد مجموعة واسعة من البكتيريا. تهدف هذه الدراسة إلى مراجعة جميع الدراسات المنشوره الخاصه بالحيوانات والانسان في الدراسات الطبيه والخاصه بالاسنان حول استخدام السبروفلوكسازين بين عامي 1995 و 2021. والمنشورات باللغة الإنجليزية، الدراسات الأصيله والمراجعات تم تضمينهاكشف العديد من الباحثين أن السبروفلوكسازين ممكن ان يسبب مرض مفصلى وان سميه الغضروف التى شوهدت فى اطفال الحيوانات قد تكون بسبب نقص المغنيسيوم المتاح وظيفيا وانتاج ضغوط التاكسد وبيروكسيد الدهون وفقدان خليه الغضروف وانخفاض فى تكوين الماده خارج الخليه ونقص فى تعبير كاسبيس 3 وماتريكس ميتالوبروتينيسسفى الانسان سبروفلوكسازين يقوم بتحفيز تمرض وتمزيق الوتر العضلى والمتابعه للاطفال الذين عولجوا بالسبروفلوكسازين اظهرت ان نسبه مئويه قليله منهم ظهرت عندهم اعراض مفصليه مرضيه حاده لها علاقه بالسبروفلوكسازين ولكنها لم تسبب اى ضرر مفصلى دائمى وان اغلب الحالات هى خفيفه الى معتدله الشده وهذه الدراسات اشارت الى ان السبروفلوكسازين قد يكون امن الاستعمال للاطفال تحت عمر 18 سنه ولكن فقط يستعمل عندما لا يكون هناك اى بديل جيد لاستخدامه حتى يتم الانتهاء من دراسات متابعه طويله الامد