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BENEFITS AND RISKS OF FLUOROQUINOLONES USE IN PEDIATRICS: A REVIEW

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ABSTRACT: Fluoroquinolones are synthetic fluorinated derivatives of nalidixic acid and are an important group of antibacterials along with the beta-lactam and macrolides are used for the treatment of various infectious diseases in adults; however, their use in children has been limited as the result of fluoroquinolone-induced musculoskeletal toxicity in animal studies. Those antibiotics are useful in the treatment of cystic fibrosis, urinary tract infections, neutropenia, gastrointestinal infections, meningitis with resistant bacteria, chronic suppurative otitis media, some cases of complicated acute otitis media, conjunctivitis, infections caused by Enterobacteriaceae (including the neonatal period), some mycobacterial infections, prophylaxis of anthrax and sepsis caused by other antibiotic-resistant organisms in pediatrics. Most of the available human studies showed the incidence of a musculoskeletal adverse event is relatively higher in fluoroquinolones than nonfluoroquinolone antibiotics; however, almost all AEs are reversible and transient. Hence, fluoroquinolones can be clinically considered in children when the benefit outweighs the possible risk.

Keywords: Fluoroquinolones, Pediatrics, Benefits, Risks

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INTRODUCTION: The development of the first quinolone, nalidixic acid, was dating back to 1962. It served as a lead compound, and structural manipulation led to the introduction of many other improved quinolone compounds. Fluoroquinolones are synthetic fluorinated derivatives of nalidixic acid and are an important group of antibacterials along with the beta-lactam and macrolides in the treatment of various infectious diseases [1].

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Despite the basic similarity in the core structure of these molecules, *i.e.* quinolone nucleus, their physicochemical properties, pharmacokinetic characteristics, and microbial activities can vary markedly across compounds attributed to the addition of fluorine atom and incorporation of other different substituents [2].

They selectively interfere with the action of bacterial topoisomerase II and IV. Inhibition of the activity of these enzymes disables DNA replication, which in turn, inhibits bacterial replication [3]. Depending on differences in the spectrum of *in-vitro* antibacterial activity, fluoroquinolones are classified into four generations. First-generation quinolones (*i.e.*, nalidixic acid, oxolinic acid, and cinoxacin) had

excellent activity against aerobic, gram-negative bacteria while the second-generation (Norfloxacin, Ciprofloxacin, Lomefloxacin, Ofloxacin, and Levofloxacin) have improved activity against aerobic gram-negative bacteria and extended modest activity on gram-positive bacteria. 3rd and 4th generation fluoroquinolones (Sparfloxacin, Gatifloxacin, Grepafloxacin, Trovafloxacin, Moxifloxacin, and Gemifloxacin) have greater potency against gram-positive bacteria, particularly pneumococci and anaerobic bacteria [4].

The fluoroquinolones have relatively high bioavailability, moderate to long elimination half-lives and distributed widely in the body fluids and tissues. There is considerable variation in elimination pattern and protein binding. Tissue concentrations often exceed plasma concentrations, while concentrations in CSF are modest in even in the presence of inflammation [5]. Even though there is scant pharmacokinetic data for fluoroquinolones from the pediatric population, evidence from previous studies showed that the systemic elimination of quinolones is faster in children than in adults; hence larger doses might be required in pediatric population excluding infants [6].

A study conducted by Chiens and his coworkers showed that Levofloxacin absorption and distribution in children were not age dependent and were comparable to those in adults. Levofloxacin elimination (reflected by $t_{1/2}$ and clearance), however, was age dependent. Children are younger than 5 years of age clear levofloxacin nearly twice as fast (intravenous dose, 0.32 ± 0.08 L/h/kg; oral dose, 0.28 ± 0.05 L/h/kg) as adults. as a result of fast clearance the area under the plasma drug concentration-time curve has been found to be approximately one half of that of the adults [7] and study were done on ciprofloxacin showed that the elimination half-life was significantly (P less than 0.001) longer in the infants (2.73 ± 0.28 h; mean ± standard deviation) than it was in the children (1.28 ± 0.52 h) [8].

Fluoroquinolones possess excellent activity against members of the family Enterobacteriaceae and other Gram-negative organisms, such as *Haemophilus influenza*, *Neisseria gonorrhoeae*, *Neisseria meningitides*, and *Moraxella catarrhalis*. They also exhibit *in-vitro* activity against methicillin-susceptible gram-positive *Staphylococcus aureus* and *Staphylococcus epidermidis*. The older quinolones are less active against streptococcal and Enterococcus species. The newer agents such as gatifloxacin, moxifloxacin, and gemifloxacin demonstrate even greater activity against Gram-positive and atypical organisms compared to levofloxacin. However, these newer agents have considerably less activity against *P. aeruginosa* than ciprofloxacin and levofloxacin [9].

Potential Indication of Fluoroquinolones in Pediatrics: Fluoroquinolones have been widely used in the treatment of various infectious diseases in adults as a result of their excellent spectrum of activity, significant tissue penetration, and convenient routes of administration. However, their use in children had been limited as a result of possible fluoroquinolone induced joint toxicity. This group of antibiotics is rapidly gaining consideration for use even in young children such as in the treatment of cystic fibrosis, urinary tract infection, gastrointestinal infection, and neutropenia, etc as new agents are emerging with a wide antimicrobial range of action and minimal toxicity [6]. Most experts, however, continue to advise against expanded fluoroquinolones use in pediatric while supporting use in selected clinical situations where the benefits outweigh the risks of therapy, and there are few other antibacterial options [10].

Fluoroquinolones in Pediatric Cystic Fibrosis: Patients with cystic fibrosis suffer from recurrent and chronic lung infections mainly caused by *Staphylococcus aureus*, *Haemophilus influenza*, and *Pseudomonas aeruginosa*. They offer the possibility of effective oral treatment for early colonization as well as chronic infections in children [11]. Ciprofloxacin is the most widely studied fluoroquinolone in pediatric patients with cystic fibrosis and is found to be safe and effective [12].

Oral and intravenous ciprofloxacin has been shown to be well tolerated in the treatment of acute pulmonary exacerbation secondary to *P. aeruginosa*. The oral dosing regimen of 40 mg/kg per day divided every 12 h, up to 2 g/day and IV ciprofloxacin 30 mg/kg /day divided every 8 hours maximum 1.2 g/day is recommended in children [13].

Ofloxacin could be an option for the treatment of cystic fibrosis as it has strong *in-vitro* activity against most *Pseudomonas* species strains, good pharmacokinetic profiles, better tolerability, and oral dose availability [14].

Fluoroquinolones in Pediatric Urinary Tract Infection: Infections of the urinary tract (UTI) occur commonly in the pediatric population. Because of the high association of pediatric UTI with congenital structural anomalies of the urinary tract and with dysfunctional elimination syndromes, it is far more common for children to be categorized as having complicated UTI than their adult counterparts. An oral antimicrobial is more convenient than parenteral therapy and is preferable as long as clinical efficacy and safety can be assured. Oral fluoroquinolones such as ciprofloxacin are an attractive alternative for the treatment of complicated UTI in children; however, safety must always be a factor in considering their use in this population [15.]

Fluoroquinolones in Pediatric Gastrointestinal Infections: Fluoroquinolones possess unique properties for treating various gastrointestinal infections. One advantage is that the oral absorption of fluoroquinolones is not affected by diarrhea. Also, high concentrations of fluoroquinolones can be maintained in the intestinal lumen for several days [16]. Fluoroquinolones have become the treatment of choice in patients with multidrug-resistant typhoid fever, and short course treatment with ofloxacin has been proven to be effective than short-course treatment with a cephalosporin, cefixime [17].

Ciprofloxacin has been used in the developing world for the treatment of pediatric intestinal infection and was proved to be safe and effective. However, there has been increasing reports of fluoroquinolone-resistant strains of *salmonella, shigella,* and *campylobacter* [6].

Fluoroquinolones in Pediatric Neutropenia: Chemotherapy-induced febrile neutropenia is a frequent event in children suffering from cancer, with high morbidity. In these situations, fluoroquinolone prophylaxis provided a significant reduction of mortality and infectious morbidities [18]. Prophylaxis with oral fluoroquinolones can reduce the incidence of gram-negative bacteremia in patients with long-standing neutropenia. Outpatient therapy with either oral ciprofloxacin or intravenous ceftriaxone for fever and neutropenia is considered effective and safe in pediatric patients [6].

Moreover, fluoroquinolones are used for the treatment of infections caused by Entero-bacteriaceae (including the neonatal period), some mycobacterial infections, methicillin-resistant Staphylococcus infection, meningitis with resistant bacteria, chronic suppurative otitis media [19], some cases of complicated acute otitis media [20], conjunctivitis [21], prophylaxis of anthrax [22] and sepsis caused by other antibiotic-resistant organisms [23, 24].

Risk of Fluoroquinolones Use in Pediatrics: The most common adverse effects (AEs) of FQs are gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Skin rashes, allergies, and photosensitivity are also frequent. Infrequently; patients develop neutropenia, eosinophilia, and elevated liver enzymes (1-4%). All of these adverse effects are typically transient and reversible with conservative management [25]. However, the most serious adverse reactions of fluoroquinolones in pediatrics are adverse musculoskeletal events, and due to fear of these events, fluoroquinolones use was once considered a contraindication in children and adolescents.

Musculoskeletal Adverse Events of Fluoroquinolones in Pediatrics: Fluoroquinolones are associated with a wide spectrum of musculoskeletal complications that involve not only tendon but also cartilage, bone, and muscle [26]. These drugs cause damage to the weight-bearing joints in juvenile animals [22]. These animals include mice, rats, dogs, marmosets, guinea pigs, rabbits, and ferrets [27]. Juvenile dogs with Quinolone Induced Arthropathy (QAP) become lame, whereas other experimental animals show no clinical signs precluding clinicopathologic correlations in those species. Lameness in dogs has been recorded as early as 2 days following initiation of quinolone dosing, exemplifying QAP's acute nature. A fluid-filled vesicle is the macroscopic feature that is pathognomic for QAP. Serosanguinous synovial effusions can accumulate in joint cavities

coincident with acute vesicle formation. It appears that the volume of synovial fluids correlates with the acuteness and severity of QAP. Complete resorption can occur by 4-week continuous treatment [28]. The mechanism that is responsible for cartilage lesion is unknown. It has been hypothesized that these lesions are caused by regression of DNA synthesis in cartilage cells, by discontinuation of mitochondrial integrity or by the clearance of magnesium from the cartilage cell surface, which disrupts the function of surface integrity that is responsible for cellular integrity of cartilage [6].

Incidence of adverse events were compared in 2523 children randomized to receive levofloxacin versus non fluoroquinolone antibiotics based on assessments by treating physicians and an independent data safety monitoring committee, events related to the musculoskeletal system were further categorized as 1 of 4 predefined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) considered most likely clinical correlates of fluoroquinolone-associated cartilage lesions observed in laboratory animals.

Levofloxacin was well tolerated during and for 1 month after therapy as evidenced by similar incidence and character of adverse events compared with non fluoroquinolone antibiotics. However, the incidence of 1 or more of the 4 predefined musculoskeletal disorders identified in non blinded, prospective evaluations, was statistically greater in levofloxacin-treated compared with comparator-treated children [29].

In a systemic review, which include 16184 pediatric patients of 105 articles, on the safety of ciprofloxacin, and there were 1065 reported AEs (risk 7%, 95% CI 3.2% to 14.0%). Out of these, 258 were musculoskeletal adverse events that occurred in 232 pediatric patients (risk 1.6%, 95% CI 0.9% to 2.6%). Arthralgia accounted for 50% of the cases. The age of occurrence of arthropathy ranged from 7 months to 17 years (median 10 years). All cases of arthropathy were resolved with management [30].

In a Study conducted to evaluate safety and efficacy of gatifloxacin in 867 children who had recurrent acute otitis media (ROM) and acute otitis media (AOM) treatment failure were treated with gatifloxacin (10 mg/kg once daily for 10 days). There was no evidence of arthrotoxicity during a one-year follow-up in any child. According to this study, gatifloxacin appears to be safe for children, with no evidence of producing arthrotoxicity.

In a randomized evaluator-blinded, active-comparator, non inferiority, multicenter study on 1650 children (6 months to <5 years) half of them received levofloxacin (10 mg/kg twice daily), and the other half received amoxicillin/clavulanate (14:1; amoxicillin 45 mg/kg twice daily) for 10 days. Safety and efficacy were evaluated within 4-6 days of therapy (visit 2), 2-5 days after completing therapy (visit 3), and 10-17 days after the last dose (visit 4). Cure rates at visit 4 were 74.9% and 73.8% in levofloxacin, and amoxicillin/clavulanate treated groups respectively, and there were no differences between the two groups regarding the frequency or type of adverse events [32]. Data from Bayer's ciprofloxacin clinical trials database also found that the incidence of arthralgia in children did not differ between the ciprofloxacin and nonquinolone antimicrobial control groups [33].

According to a safety report in 1795 children who received 2030 treatment courses of intravenous (average dose of 8 mg/kg/day) or oral (average dose of 25 mg/kg/day) ciprofloxacin arthralgia occurred in 31 ciprofloxacin treatment courses (1.5%) and the majority of events was of mild to moderate severity and resolved without intervention. More than 60% of arthralgia episodes were in children with cystic fibrosis [34]. In a trial performed in 144 children (aged 0.5-16) with mucoviscidosis and 37 children (aged 1.75-15) with aplastic anemia: patients with mucoviscidosis were treated with fluoroquinolones (such as ciprofloxacin, ofloxacin, and pefloxacin) followed by repeated short courses in combination with other antibacterials while patients with aplastic anemia were treated permanently for a long time with low doses of fluoroquinolones as monotherapy for autoinfection prophylaxis.

The analysis was performed on the base of catamnesis, year growth rate, and postmortal morphological investigation of the right knee joint.

It was shown that development of arthropathy didn't depend on treatment duration, as it developed during the first three weeks of the fluoroquinolone use, but it was found to be dependent on the fluoroquinolone type, patient age, and nosology. The arthropathy had a favourable prognosis and was fully resolved at the period from 7 days to 3 months according to the arthropathy form (arthrologic, arthritic) [35].

In an observational prospective study on 116 neonates who received ciprofloxacin and 100 neonates who did not receive ciprofloxacin. The growth at the end of the first year of life was evaluated in 77 of those who received ciprofloxacin and 83 infants of control groups. No significant differences between the two groups were found in growth at the end of the first year of life. Also, no clinical evidence of arthropathy was observed [23].

Bradley *et al.,* investigated musculoskeletal toxicity of Levofloxacin in 2233 subjects participating in the 12-month follow-up study, 124(9%) of 1340 who received levofloxacin, and 83(9%) of 893 comparator subjects were continued for 5-year post-treatment assessment. From children identified with a musculoskeletal AEs during years 2 through 5 post-treatment, the number that was "possibly related" to drug therapy was equal for both arms: 1 of 1340 for levofloxacin and 1 of 893 for the comparator.

Of all cases of musculoskeletal AEs assessed by the Data Safety and Monitoring Committee at 5 years' post-treatment, no case was assessed as "likely related" to study drug and this study concluded that risks of cartilage injury with levofloxacin appear to be uncommon, are clinically undetectable during 5 years or are reversible [36].

CONCLUSION: Fluoroquinolones are one of the most widely used antibacterials in adults. However, their use in children has been restricted due to animal reports of joint toxicity. Despite the paucity of data on these AE in children, those few previous studies showed no significant increase in musculoskeletal toxicity. Therefore, it is judicious to consider the impact of recommending these drugs in the pediatric population to treat life-threatening and multi-drug resistant infections, and potentially other possible indications.

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