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Fluoroquinolone Use in Children: the Benefits and Risks

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Summary

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Background: Fluoroquinolones are widely used in the treatment of various infectious diseases in adults because of their broad spectrum of activity, their significant tissue penetration and the availability of oral formulations. Their use in children has however, been limited until recently as a result of possible fluoroquinolone-induced joint toxicity. Nevertheless, these agents are rapidly gaining consideration for use in children as new agents are emerging with wider spectrum of action and minimal toxicity, even in young children.

Objectives: This review presents the pharmacokinetics, clinical indications, and possible toxicity and safety profiles of fluoroquinolone in children.

Methods: A MEDLINE search for systematic reviews and original publications on (a) fluoroquinolone use in adults, children and animals, (b) clinical trials of fluoroquinolones in adults, and (c)pharmacokinetics, efficacy and safety of the drugs in children, was undertaken using *Index Medicus* and *PubMed*. Abstracts from the searches were read to determine their relevance and in most cases, the original article was sourced to provide further information.

Results: The search yielded 23 relevant articles (three reviews, four clinical trials and 16 original research work).

Conclusion: When a particular antibiotic therapy fails or cannot be tolerated, the use of fluoroquinolones should be seriously considered as the potential benefits of their use may outweigh concerns about safety and antimicrobial resistance.

Introduction

NALIDIXIC acid, developed in the 1960s, was the first quinolone used to treat urinary tract infections.[1,2] During the past 40 years, numerous modifications have been made to this antimicrobial to develop the fluoroquinolones which have improved antimicrobial, pharmacokinetic and therapeutic properties. The early fluoroquinolones (ofloxacin, pefloxacin, and ciprofloxacin) have a spectrum of activity that covers both gram-positive and gram-negative pathogens.[3-5] In the past, the use of fluoroquinolones was restricted because of concern for potential cartilage damage. However, their use has been on the increase during the past decade in many parts of the world. They have progressively become a mainstay in the treatment of serious bacterial infections particularly in adults. However, following early studies of the drugs in different immature animal models demonstrating serious cartilage erosion and joint malformations,[6-11] these agents were considered to be contraindicated in children.[12,13] In spite of this, fluoroquinolones have been used in paediatric patients in selected cases. Available data in children are largely the result of ciprofloxacin use in selected patients with pulmonary infection, (especially ystic fibrosis), chronic suppurative otitis media, complicated urinary tract infection, uncomplicated gonorrhoea, life-threatening salmonellosis and shigellosis, antimicrobial-resistant meningitis, multidrug- resistant tuberculosis, and central nervous system (CNS) infection - conditions in which the potential benefit was thought to outweigh the risk.[12-16]

Most of the available data on the use of fluoroquinolones in children are from developed countries. Few developing countries, such as India, are beginning to use ciprofloxacin to treat resistant neonatal sepsis resulting from gram-negative bacteria, even in the very low birth weight premature babies, a group at high risk of developing impaired linear growth[17] and in the treatment of acute osteomyelitis in children with sickle cell disease in Togo.[18] Results emanating from such studies have been very encouraging. Ciprofloxacin has been shown not to

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have effect on linear growth in infancy.[17] In Africa, literature is sparse on the use of fluoroquinolones in children, however, it has been reported in Nigeria that most of the gram-positive and gram- negative bacteria causing pyogenic meningitis in children are 100 percent sensitive to ciprofloxacin.[16]

The gradual emergence of bacterial resistance to antibiotics used to treat most of the childhood infectious diseases in the developing countries, the high cost of the third generation cephalosporins which are alternatives, lack of oral formulations of the third generation cephalosporins, and longer duration of hospital admission, necessitate the search for alternative antimicrobial agents such as the fluoroquinolones. This article reviews the evidence of the safety and risks of the fluoroquinolones in all paediatric age groups.

Mechanism and Spectrum of Activity

The fluoroquinolones are bactericidal agents that act by interfering with the enzyme DNA gyrase to inhibit bacterial DNA synthesis.[19] They have a very broad spectrum antibacterial activity, being effective against most gram-negative organisms, including *Pseudomonas aeruginosa*, acinetobacter, campylobacter, haemophilus, salmonella, shigella, klebsiella, and escherichia species.[17, 20] Gram-positive coverage includes most species of staphylococcus and streptococcus, including many beta-lactam resistant strains. The early fluoroquinolones were generally inactive against anaerobes. In addition to their broad spectrum activity against the gram-negative and gram-positive bacteria, some of the recently marketed fluoroquinolones have an expanded activity against enterococci and the anaerobes.[21-25]

Pharmacokinetics

Most of the fluoroquinolones are well absorbed following oral administration, with excellent tissue penetration, and long half-lives.[26,28] They are excreted unchanged in the urine.[18] However, pharmacokinetic data on fluoroquinolone are limited in children as a consequence of their restricted use. The scanty data available in children are on ciprofloxacin, ofloxacin, trovafloxacin, gatifloxacin, and moxifloxacin.

Ciprofloxacin

In 1992, Peltoba *et al* studied 16 healthy children (seven infants, nine children), all less than six years of age, treated with a single oral dose (15mg/kg) of ciprofloxacin.[29] They reported a mean peak concentration (C_{max}) value of 3.3 mg/L and 2.1mg/L in infants and children respectively, while the mean time to reach C_{max} (t_{max}) was 1.18 and 1.0 hours, respectively. There was no statistically significant difference in the C_{max} or t_{max} between the two groups. The area under the curve (AUC) was greater in infants (16.1 mg*h/L) than in children (5.3 mg*h/L). A mean elimination half-life ($t_{½}$) of 2.73 and 1.28 hours were reported in infants and children, respectively. Ciprofloxacin elimination half-life $t_{½}$ in children seemed shorter than in adults (4-5 hours). Therefore, they suggested increasing the frequency of oral ciprofloxacin to three times daily in children aged 1-5 years.

The pharmacokinetics of ciprofloxacin in children with cystic fibrosis (CF) has been evaluated in two studies. In 1996, Schaefer and co-workers studied the disposition of ciprofloxacin in 10 children, aged one to six years, with CF.[30] The patients received intravenous infusions of 10mg/kg ciprofloxacin every 12 hours in two doses, followed by oral administration of 15mg/kg every 12 hours. The mean C_{max} values were 8.5 and 8.3 mg/L after the first and second intravenous infusions, respectively, and 3.5 mg/L after the oral dose. Thirty four percent of ciprofloxacin was protein bound as seen in the adults. In a second study carried out in 1997, Rubio *et al* studied the disposition of ciprofloxacin in 18 children, aged five to 17 years with CF.[31] The patients received 10 mg/kg ciprofloxacin IV every eight hours for at least three days, and were then switched to 20 mg/kg ciprofloxacin orally every 12 hours. Mean half-life values for the group were 2.6 ± 0.6 hours with IV dosing and 3.4 ± 0.7 hours with oral dosing. Subgroup analysis revealed no significant difference in elimination between the younger and older children.

In another study in 1998, using an investigational ciprofloxacin oral suspension in 16 healthy children, aged 0.3 to 7.1 years,[32] and administering 10 mg/kg of the drug every eight hours, Peltoba *et al* reported a non-significantly different half-life values among the subgroups, with values ranging from 4.21 ± 1.1 hours in patients aged one year, to 5.1 ± 1.1 hours in children aged two to five years. The results of these studies suggest that ciprofloxacin pharmacokinetic parameters in children are similar to values established in adults.

Ofloxacin

The pharmacokinetics of oral and intravenous ofloxacin was studied in 17 patients with typhoid fever, aged five to 14 years.[33] Seven patients received 7.5 mg/kg ofloxacin orally followed by 7.5 mg/kg IV over 30 minutes, 10 patients received 7.5 mg/kg ofloxacin IV then orally. The mean oral bioavailability was 91 percent, similar to that of a healthy adult. The mean C_{max} ofloxacin was significantly higher after a single oral dose (5.5mg/L). The AUC values were 34.13 and 32.32 mg*h/L following a single IV and oral doses, respectively. The mean t_{max} values following single IV and oral doses were 0.5 and 1.69

hours, respectively. The mean apparent volume of distribution was 1.28 L/kg. The order of the route of administration (IV first or oral first) had no significant effect on the C_{max}, t_{max} or AUC.

Trovafloxacin

Trovafloxacin pharmacokinetic properties have also been studied in infants and children.[34] Six infants, aged three to 12 months, and 14 children, aged 1.7 to 12.5 years, were given IV alatrofloxacin (prodrug of trovafloxacin) 4 mg/kg as a single dose. The mean total clearance, volume of distribution, and elimination half-life in the older children were 0.135 L/h/kg, 1.74 L/kg and 9.42 hours, respectively; the corresponding values in infants were 0.158 L/h/kg, 1.72 L/kg, and 8.25 hours, respectively. The pharmacokinetics in infants and children were similar.

Moxifloxacin and Gatifloxacin

The disposition of gatifloxacin was studied in 76 children, aged between six months and 16 years.[34] Infants and young children received a single oral dose of gatifloxacin suspension in an escalating dosage of 5, 10, or 15mg/kg (maximum of 600mg); older children received tablet formulation at a dose of 10mg/kg. Gatifloxacin's apparent clearance and half-life were 5.5 ± 2.1ml/min/kg and 5.1±1.4h. The maximum plasma concentration of the drug and area under the curve (AUC) increased in a manner approximately proportional to the dose. At the 10mg/kg/dose, the bioavailability was similar between the suspension and tablet formulation. The apparent oral clearance of gatifloxacin, normalized for body weight, exhibited a small but statistically significant decrease with increasing age. In all subjects receiving gatifloxacin at 10mg/kg, the AUC exceeded 20μg*h/ml, suggesting that gatifloxacin at this dose every 24h will achieve therapeutic concentrations in plasma in infants and children.

Clinical Usefulness and Advantages

In children, the fluoroquinolones represent a new class of antimicrobials with a number of inherent advantages. However, their usefulness in children was initially restricted by the potential for these agents to induce cartilage toxicity in immature animals.[6-11] Of recent, several studies have shown that the arthrogenic effects of the fluoroquinolones appear to be species-specific and drug-dependent.[9] No such arthropathy has been reported in children after the use of ciprofloxacin,[17] levofloxacin, gatifloxacin, or moxifloxacin. Therefore, paediatricians are increasingly encouraged to use this group of drugs although with caution, in infants and children.

In addition to their excellent pharmacokinetic properties, they are available in both oral and parenteral formulations. Therefore, they offer a therapeutic alternative to the commonly used antimicrobials in a number of clinical situations for which there have been limited options (Table I). These drugs have been used in a number of these clinical situations in infants and children, with beneficial effects reported.[15,17,18,30,35-53] Ofloxacin (15 mg/kg/day), ciprofloxacin and levofloxacin (both taken as 20 to 30 mg/kg/day) in two or three divided doses, are the most commonly used agents. Gatifloxacin is effective and tolerable at a dose of 10mg/kg, once daily.

Table I

Conditions in which Fluoroquinolones use may be considered in Children

- Osteomyelitis caused by *Pseudomonas aeruginosa* or other Gram negative bacteria
- Acute otitis media or externa
- Drug allergy (eg to β-lactams or macrolides)
- Complicated urinary tract infection
- Sexually transmitted infection (in adolescents and older children)
- Persistent fever in immunocompromised children treated with a β-lactam antimicrobial with or without an aminoglycoside
- Recurrent or persistent infection despite seemingly adequate treatment with more conventional agents
- Life threatening salmonellosis or shigellosis

Disadvantages

Resistance to Fluoroquinolones

Data suggest that increased use of a given class of antimicrobials leads to increased resistance in that class.[54,55] There have been several reports in recent years of growing bacterial resistance to fluoroquinolones, especially by *Streptococcus pneumoniae*.[54,56] A major concern therefore with expanding the scope of fluoroquinolone therapy to include paediatric indications is the potential problem of increased fluoroquinolone resistance due to an increase in drug pressure among strains of S pneumoniae, a common community-acquired respiratory pathogen.[55,57,58] It is also commonly implicated in meningitis and bacteremia.[59]

Adverse effects

The safety profiles of fluoroquinolones in adults are well established. Although there are limited safety data in children, the incidence of adverse events with ciprofloxacin in children is similar to that in adults;[60] it is therefore possible to extrapolate adverse events observed in adults to children. The most commonly reported adverse events associated with the fluoroquinolones for both paediatric and adult patients include musculoskeletal, gastrointestinal, central nervous system (CNS), dermatological, and hepatic effects. The majority of these adverse events are mild and reversible. Dysglycaemia is another adverse effect that may necessitate hospital admission.

* Musculoskeletal

The greatest concern with fluoroquinolone use in children is potential bone and joint damage. In animal models, the fluoroquinolones have been associated with a slowly progressive arthropathy characterized by fluid-filled blisters, fissures, and erosions within the joints.[13] The mechanism for this adverse effect is still unclear, but may involve alterations in the collagen deposition and changes in chondrocyte function.[61] While the risk for joint damage has caused clinicians to be cautious when prescribing these agents in children, close monitoring of paediatric patients treated with fluoroquinolones has thus far, failed to reveal any significant cartilage toxicity, except pefloxacin that has been reported to be associated with joint pain or swelling in the weight bearing joints (knees, hips, shoulders).[62-70]

* Gastrointestinal

Most antimicrobials cause varying degrees of gastrointestinal adverse events in children. Low incidences of these events have been reported in children when using some common antimicrobials.[71,72] The estimated incidence of gastrointestinal adverse events following fluoroquinolone use is between 2 and 20 percent, with the most common symptoms being nausea, anorexia, or dyspepsia. Abdominal pain, vomiting, and diarrhoea also occur and may be more severe. Paediatric clinical trials of ciprofloxacin have reported incidences of gastrointestinal adverse events, including nausea, vomiting, diarrhoea and abdominal pains, ranging from 4.3 to 16.4 percent.[36,39,41] Gatifloxacin and moxifloxacin are associated with the highest incidence of nausea and diarrhoea among the fluoroquinolones. The high rate of vomiting with gatifloxacin may be associated with its liquid formulation, which is not very palatable.

* Central Nervous System (CNS)

Adverse events involving the CNS constitute the second most common adverse events reported in patients receiving fluoroquinolones. They occur in 1-2 percent of adult patients taking fluoroquinolones.[73] The most common symptoms among adult patients are headache, dizziness, and drowsiness. Other disturbances include sleep disorders (restlessness and insomnia), agitation, confusion, delirium, psychosis, tremor, seizure, and visual disturbances.[73,74] Up to 4.8 percent incidence of CNS adverse events with the use of ciprofloxacin in children has been reported.[39-41] The potential for CNS adverse drug events in children is of concern since the extent to which these effects can influence school performance, language skills and other learning processes are not known.

* Dermatological

In paediatric clinical trials with ciprofloxacin, dermatological adverse events including rash, urticaria, and pruritus, occurred in 2.4 to 15 percent of patients younger than 18 years.[36,39-41] Photophobic reactions, ranging from mild erythema to bullous eruptions have been reported with ciprofloxacin and levofloxacin than with moxifloxacin or gatifloxacin.[62] Less common dermatological adverse effects include oedema, haemorrhagic bullae, erythema multiforme, vasculitis, and dermatitis.[39,74]

* Dysglycaemia

This condition manifests either as hypo- or hyperglycaemia, another potentially fatal side effect of the fluoroquinolones.[75] From inception, fluoroquinolones were known to affect glucose metabolism. Even though the available literature focused on adults,[76-79] the paediatric age groups were not totally excluded from this problem. Dysglycaemia requiring hospitalisation has been reported with the use of different forms of fluoroquinolones at therapeutic dose,[76] with an incidence rate of 1.1 percent from gatifloxacin. Compared with gatifloxacin, rates were substantially lower for ciprofloxacin (0.3 percent), levofloxacin (0.3 percent), and moxifloxacin (0.2 percent).[75,76] In Canada, it has

been reported that out of 28 cases of gatifloxacin-induced dysglycaemia, two deaths occurred and 89 percent of the affected patients had pre-existing diabetes mellitus and 67 percent were hypoglycaemic events.[75,79] Hyperglycaemia due to fluoroquinolones on the other hand, is likely to be due to overdosage or a toxic effect of the drug in patients with concomitant renal insufficiency.[80] Hyperglycaemia occurs more often than hypoglycaemia and gatifloxacin has been reported to have the highest risk. [75]

* **Others**

Transient elevations in the values of liver function tests or serum creatinine[81] and rarely, greenish discolouration of the teeth.[82]

Drug Interactions

Fluoroquinolones interact with many other medications and nutrients (Tables II and III). A large percentage of these interactions are the result of interference with cytochrome P450 1A2 function.[18] Fluoroquinolones should not be taken simultaneously with enteral feedings. Patients may take fluoroquinolones with food, but should be instructed to avoid taking dairy products such as milk and yoghurt, iron or zinc supplements at the same time as a fluoroquinolone dose.[83] Multivalent cations such as calcium, magnesium, aluminium, iron and zinc impair absorption of fluoroquinolones. Dairy products and antacids are rich in calcium, magnesium and aluminium,[84] while iron is routinely used in some children in Nigeria as *blood tonic*,[85] zinc supplements are also used in various childhood ailments such as diarrhoea,[86] pneumonia[87] and malaria.[88] These multivalent cations can form insoluble complexes in the gut if taken simultaneously with fluoroquinolones.[89] Studies have shown that the absorption of fluoroquinolones is reduced by 60-75 percent when used simultaneously with multivalent cations.[89] Therefore, patients should stop taking products containing these cations until fluoroquinolones therapy has been completed. If withholding therapy is not feasible, the fluoroquinolones and cation products should be administered at least, two hours apart.

Table II

Effects of other Drugs on the Fluoroquinolones

Drugs	*Effects*
Antacids	Impair absorption
Antineoplastics	Increases serum concentration
Azlocillin	Decreases clearance[a]
Cimetidine	Decreases clearance[a]
Probenecid	Decreases clearance[a]

[a] increases serum concentrations of fluoroquinolones

Conclusion

The widespread use of fluoroquinolones by many paediatric patients may promote the adverse events and the development of resistance, and ultimately limit the usefulness of these agents. Furthermore, the availability of many safe and effective antimicrobials for paediatric patients precludes the need to currently introduce fluoroquinolones as first-line treatment of non-life-threatening infections. These agents should be reserved for patients in whom other antimicrobial therapies have failed or in those who are allergic to â-lactams or macrolides. It is advised that their use be reserved for the treatment of severe infections such as gastrointestinal infections caused by salmonella or shigella, for which few alternative antimicrobial agents are available, and in situations where the potential benefit of fluoroquinolone use may outweigh concerns about safety and antimicrobial resistance. Physicians may feel constrained to use these agents even in these situations, because of the absence of labelling for these drugs in paediatric patients and the warning that appears on some existing labels concerning the development of arthropathy in young animals. Although these concerns are genuine, the off-label use of drugs in paediatric patients is common and often justifiable.[76]

Table III

Effects of the Fluoroquinolones on other Drugs

Drugs	*Effects*
Caffeine	Decreases clearance
Cyclosporine	Nephrotoxicity risk
Phenytoin	Increases serum concentration
Theophylline	Decreases clearance
Warfarin	effect

[**] Increases serum concentration of the affected drug

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