

Fluoroquinolones in Pediatrics

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Abstract: The fluoroquinolones (FQ) are a group of antimicrobials with a broad spectrum of activity against gram positive and gram negative organisms, intracellular and anaerobic organisms. These antimicrobial agents have excellent oral bioavailability, high tissue penetration, low protein binding and a long elimination half life. The experience with these antibiotics in children has been limited to certain conditions mainly in the treatment of bronchopulmonary exacerbations in children with cystic fibrosis and in the ambulatory treatment of children with fever and neutropenia. Despite the limited use, it is recognize that there are other potential indications for the use of FQ in pediatrics such as for the treatment of children with bacterial meningitis, refractory and recurrent otitis media, pneumonia, multiply resistant salmonellosis and shigellosis and complicated urinary tract infections. Furthermore, the new FQ have shown excellent in-vitro activity against penicillin-resistant *Streptococcus pneumoniae* suggesting that these agents may be an attractive alternative for the treatment of conditions that involve these problematic strains. Cartilage toxicity due to FQ had been a major concern however; the previous experience with ciprofloxacin and recently the results from long term (12 months) prospective studies have found no evidence of such a problem in children. Ciprofloxacin was recently approved for the treatment of children with complicated urinary tract infections. If based on the safety and clinical results of ongoing clinical trials, other new FQ are approved for the treatment of other conditions in children, particularly respiratory tract diseases, caution is highly recommended to avoid selection of bacterial resistance.

Key Words: Fluoroquinolone, pharmacology, febrile neutropenia, otitis media, bacterial meningitis, gastrointestinal infections.

INTRODUCTION

Since the discovery of nalidixic acid, the first known quinolone in 1962, various chemical groups have been added to the quinolone nucleus producing new and improved fluorinated quinolones. The fluoroquinolones have a broad bacterial in-vitro activity suggesting that these agents have a particular place in the empiric treatment of severe diseases with mixed pathogens and in the treatment of conditions where resistant pathogens are suspected.

The use of fluoroquinolones in pediatrics has been limited mainly because of concerns about joint or bone toxicity seen in preclinical studies with juvenile animal models [1, 2]. Despite these observations, fluoroquinolones are used in children [3]. In year 2002, the "off-label" use of quinolones in children in the United States was estimated in 2.7 million prescriptions, with 300,000 doses prescribed for the treatment of children less than 24 months of age [3,4].

In 1989 the Food and Drug Administration (F.D.A.) agreed upon the possibility of performing controlled clinical trials with quinolones in pediatric patients, particularly in those patients with cystic fibrosis (CF), febrile neutropenia and with severe *Salmonella* infections. The suggested scope of the pediatric trials was to evaluate the clinical efficacy and short and long term safety of fluoroquinolone therapy in children. This review summarizes current data, from MEDLINE and other scientific sources, about the role of fluoroquinolones in pediatric patients and the accumulated evidence about the safety of these components.

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PHARMACOLOGY OF FLUOROQUINOLONES IN PEDIATRICS

In adults, fluoroquinolones have a rapid oral absorption with an average bioavailability of 95%, a long elimination half life, low protein binding and high tissue penetration, being almost exclusively eliminated unchanged by the urine [5]. Information about the pharmacology of fluoroquinolones in pediatrics is limited and most of the data is derived from studies in patients with CF and from individual studies of specific quinolones [6]. In children, fluoroquinolones share most of the pharmacologic characteristics with adults and this includes an excellent bioavailability, a long elimination half life, high volumes of distribution, low protein binding and renal excretion [6-8]. In pediatric patients, most of the pharmacokinetic studies performed were initially with ciprofloxacin and recently with levofloxacin, trovafloxacin and gatifloxacin.

In the case of ciprofloxacin, published studies have shown that after a single oral dose, drug absorption is rapid. Mean maximum serum concentrations (C_{max}) are reached within one hour with values varying from 2.1 to 3.3 mg/L [7]. These studies have also shown that the half life of ciprofloxacin is age dependent being longer in children younger than 12 months of age (T_{1/2} = 2.73±0.28h) than in children older than 12 months of age (T_{1/2} = 1.28±0.52h) [6].

In another published study the pharmacokinetics of levofloxacin were evaluated in children between the ages of 6 months and 16 years of age following a single intravenous or oral dose of levofloxacin at 7 mg/kg [9]. The results of this study showed that drug absorption was not age dependent, that the oral and intravenous formulations share comparable areas under the plasma drug concentration-time curve and drug elimination was found to be age dependent with children younger than 5 years of age showing a

clearance twice as fast as that seen in adults. Based on these pharmacologic parameters, a once-daily oral dose of 10 mg/kg of levofloxacin was suggested for children older than 5 years of age and a dose of 10 mg/kg twice a day for children younger than 5 years.

The pharmacology of trovafloxacin in children has also been analyzed in two clinical trials [10,11]. The results of these studies indicated that a dose of 4 mg/kg is required to achieve serum levels similar to those achieved after a 300 mg intravenous dose of trovafloxacin in adults and that cerebrospinal fluid (CSF) concentrations were approximately 25% of the serum levels with peak CSF levels above the minimum inhibitory concentration (MIC) of most pathogens involved in the etiology of bacterial meningitis in children. One interesting characteristic of this compound is that, unlike the other quinolones, 95% of the antibiotic is excreted through the biliary tract.

The pharmacokinetics of gatifloxacin in children has also been studied. In one study, oral gatifloxacin given in children at a dose of 10 mg/kg, achieved therapeutic concentrations in plasma similar to those achieved after an oral dose of 400 mg of gatifloxacin in adults (4.0 ug/ml versus 4.1 ug/ml, respectively) [12]. Cmax and AUC of gatifloxacin increased in a proportional manner to the dose given and oral gatifloxacin showed decreased clearance with increasing age and urine excretion at 24 hours showed 65% of the administered dose unchanged. All subjects that received a 10 mg/kg dose of gatifloxacin, achieved predicted free area under the concentration-time curve / minimum inhibitory concentration ratios (AUC/MIC) greater than 34 for typical *S. pneumoniae* isolates and greater than 250 for *H. influenzae* and *M. catarrhalis*. With the exception of some gastrointestinal disturbances, gatifloxacin was safe and well tolerated. Studies in meningitis experimental models have also shown excellent CSF penetration (25%) of gatifloxacin in the rabbit animal model [13].

ANTIMICROBIAL ACTIVITY

Fluoroquinolones are a family of antibiotics with an extended spectrum of antimicrobial activity (Table 1) [14-16]. The addition of chemical groups to the original quinolone

nucleus has allowed the development of different levels of increasing quinolone bacterial activity [17]. Antimicrobial activity of the first-generation fluoroquinolones (nalidixic acid) is high against aerobic Gram-negative bacteria including most enterobacteria; however, the activity against aerobic Gram-positive bacteria is poor [18]. Second generation fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin and levofloxacin) show improved activity against Gram-negative bacteria, including excellent activity against *Pseudomonas aeruginosa* (particularly in the case of ciprofloxacin) and added activity against aerobic Gram-positive bacteria with poor activity against anaerobic pathogens [19].

The addition of third generation fluoroquinolones (grepafloxacin, sparfloxacin, temafloxacin, tosufloxacin, pazufloxacin) added activity against anaerobes and greater potency against aerobic Gram-positive bacteria, particularly against *Streptococcus pneumoniae*, and the newer fourth generation fluoroquinolones (gatifloxacin, trovafloxacin, gemifloxacin, moxifloxacin) show potent activity against anaerobes and an impressive activity against *Streptococcus pneumoniae*, including penicillin and cephalosporin resistant isolates [15, 20, 21].

CYSTIC FIBROSIS

Because *Pseudomonas aeruginosa* is one of the most common pathogens detected in CF patients with bronchopulmonary exacerbations and because ciprofloxacin has excellent in-vitro activity against this pathogen, many studies evaluating the safety and clinical success rates of this agent have been performed in CF children [22-24].

In one of the initial studies, the pharmacokinetics of ciprofloxacin in children with CF was characterized [6]. This study demonstrated the absence of pronounced changes in either the AUC or the Cmax of ciprofloxacin in children with CF when compared to reported data on healthy adults. However, a higher clearance of ciprofloxacin was observed in children, when compared to healthy adults, suggesting the need of higher intravenous and oral ciprofloxacin doses (30 mg/kg/day and 40 mg/kg/day, respectively) in CF children than the ones recommended for adults.

Table 1. Antibacterial Spectrum of Quinolones [14-16]

Quinolone	Aerobic Gram Positive Bacteria	Aerobic Gram Negative Bacteria	Anaerobic Bacteria
Nalidixic Acid	-	++	-
Norfloxacin	+	+++	-
Ciprofloxacin	+	+++	-
Levofloxacin	++	+++	-
Gatifloxacin	+++	+++	++
Trovafloxacin	+++	+++	+++
Moxifloxacin	+++	+++	+++
Gemifloxacin	+++	+++	+++

- poor activity, + mild activity, ++ moderate activity, +++ excellent activity.

There have been various clinical trials in pediatric patients with CF comparing sequential ciprofloxacin therapy (intravenous followed by oral treatment) versus the standard antimicrobial combination of intravenous ceftazidime plus intravenous tobramycin [23,24]. The results of these studies suggest that the clinical response, based on clinical and pulmonary function test improvement, were similar in the two groups with one study showing a higher transient reduction in colonization with *P. aeruginosa* in the group of patients treated with ciprofloxacin versus patients treated with ceftazidime plus tobramycin (24% versus 63% respectively, $p=0$). In these trials, the percentage of drug related adverse events were similar with both regimens; additionally, close observation to cartilage toxicity in patients treated with ciprofloxacin did not show any data of toxicity and furthermore, autopsy studies from CF children that received multiple courses of ciprofloxacin failed to find quinolone related alterations in bone or joint cartilage as those seen in experimental animal models [25].

Ciprofloxacin has also been evaluated as a three month outpatient, maintenance therapy in CF children (age range 8 – 25 years) [26]. Although in this trial ciprofloxacin proved to be efficacious, safe and well tolerated, selection of ciprofloxacin resistance was observed in 23% (7/31) of *P. aeruginosa* isolates, suggesting the need to further evaluate the value of maintenance therapy versus the potential for selection of resistance.

FEBRILE NEUTROPENIA

The onset of fever in a neutropenic patient suggests a potentially serious infection and it has been estimated that approximately 50% of neutropenic patients who become febrile have an infection and that 85% of isolated microorganisms are bacterial pathogens originated, in the majority of cases, from the patient's own intestinal flora [27,28]. For more than 30 years, the management of febrile neutropenic patients was traditionally limited to urgent in-hospital treatment with combination therapy with two or more antibiotics (usually a beta-lactam plus an aminoglycoside) as well as monotherapy with extended spectrum agents (usually third generation cephalosporins, antipseudomonal penicillins or carbapenems) [29-31]. However, this practice was based on the notion that all febrile neutropenic patients have a predisposition to severe infection with high morbidity and mortality [32,33]. Over the past decade, it has become evident that neutropenic cancer patients are not a homogeneous group and that management may vary depending on their risk factor status [34,35]. Currently, febrile neutropenic patients are stratified into high-risk or low-risk groups and different treatment options have been proposed [36-38].

Low risk febrile neutropenia is defined by the National Cancer Institute criteria as those patients with less than 10-day duration of neutropenia, who are hemodynamically stable, without new pulmonary infiltrates, abdominal pain, nausea, vomiting or mental status changes [39,40]. This group of patients represents those children in whom outpatient antibiotics may be considered when they become febrile.

Initially, due to their broad antibacterial spectrum and favorable pharmacokinetic behavior, monotherapy with oral

quinolones had been considered an alternative for the treatment of febrile neutropenic patients regardless of their risk factors [41-43]. These studies with intravenous ciprofloxacin showed poor clinical response rates in patients with Gram-positive infections and an increased risk of breakthrough Gram-positive bacteremias, particularly secondary to alpha-hemolytic *Streptococcus* and coagulase negative *Staphylococcus* [44-46].

Later on, Rubenstein *et al.* randomly treated 83 episodes of low risk febrile neutropenia with combined therapy; oral ciprofloxacin plus clindamycin or intravenous aztreonam plus clindamycin [47]. Results from this trial demonstrated good clinical efficacy in both groups (88% versus 91% response rates, respectively) with no mortality.

More recently, a clinical trial in low risk febrile neutropenic children older than 2 years of age was completed [48]. The objective of this study was to compare the clinical success rates of intravenous ceftazidime (50 mg/kg/dose, every 8 hours) versus oral ciprofloxacin (12.5 mg/kg/dose, every 12 hours) used on an outpatient basis. The overall clinical success was 86% with no statistically significant differences among patients treated with oral ciprofloxacin (80%) or intravenous ceftazidime (94%) ($p=0.1$). Additionally, no significant differences were found in the duration of fever (average 2.7 days) or treatment duration (average 4.7 days) and modification of therapy was not required in most cases (77%).

Another study performed in patients 5 years to 74 years old, compared the efficacy of oral therapy with ciprofloxacin plus amoxicillin/clavulanate versus intravenous ceftazidime monotherapy for the treatment of low risk febrile neutropenic patients [49]. Even though the majority of subjects in this study were adults the results were encouraging. Clinical success without the need for modification of therapy was seen in 71% of the oral group versus 67% in the intravenous group. Duration of neutropenia was 3.4 days versus 3.8 days, respectively. The overall incidence of intolerance to oral antibiotics was 16% versus 1% in the intravenous group. In this study oral therapy with ciprofloxacin plus amoxicillin/clavulanate proved to be as effective as intravenous therapy.

Prophylaxis for bacteremia in immunosuppressed patients treated with fluoroquinolones has also been studied in several trials [50-52]. The results of these studies showed a tendency towards a marked decrease in infections caused by Gram-negative bacteria, however, Gram-positive bacterial super infections, particularly by *Streptococci viridians* and *Staphylococcus aureus* were a major concern. Because of these findings, fluoroquinolone prophylaxis is currently not routinely recommended in these patients.

The distinction of the different risk levels in febrile neutropenia has allowed the identification of a group of patients that may benefit from oral fluoroquinolone therapy. Oral therapy offers a number of advantages including total lower cost, improved quality of life and a decreased risk for nosocomial infections. Fluoroquinolones have shown efficacy and safety in the treatment of these patients when given as oral monotherapy in low risk patients or as part of combination therapy on high risk patients.

GASTROINTESTINAL INFECTIONS

World-wide, infectious diarrhea is one of the most frequent infectious diseases in children causing an estimated 2 million deaths every year in developing countries, the majority in children younger than 5 years of age [53]. The most common bacterial agents associated with invasive diarrhea in children are *Shigella sp.*, *Salmonella sp.*, *Campylobacter sp.*, and enteroinvasive *E. coli*. Although often unnecessary in simple cases, antimicrobials are useful when risk factors like young age, malnourishment, dehydration or severe underlying disease are present. In such cases, antimicrobial therapy should be given to ensure the best clinical response. Furthermore, therapy, in these cases, may shorten the duration of symptoms, decrease the shedding of bacteria and prevent complications such as sepsis or protracted diarrhea [54].

Current therapies for shigellosis have been complicated by the recent emergence of resistance to ampicillin, trimethoprim-sulfamethoxazole and nalidixic acid [55]. In the case of *Salmonella sp.* acute gastroenteritis, first and second generation cephalosporins are many times ineffective [56] and *Campylobacter sp.* infections are treated with erythromycin; however, this antibiotic is not active against the rest of the enteric pathogens and has many gastrointestinal side effects. Lastly, the treatment of enteroinvasive *E. coli* has been compromised by the same increasingly resistant conditions affecting the management of *Shigella sp.* [56,57].

Both, the emergence of resistance among enteric pathogens to currently used antibiotics and the susceptibility of some pathogens to specific narrow spectrum antibiotics, has reduced the availability to define first line empiric therapies in pediatric invasive diarrhea and usually intramuscular ceftriaxone is used as empiric treatment for many of these infections [58]. The broad activity of fluoroquinolones against enteric Gram-negative bacteria including, those resistant to commonly used antibiotics, appoint them as an attractive alternative for the management of gastrointestinal infections [59].

The efficacy and safety of ciprofloxacin, in the treatment of invasive diarrhea in children, has been analyzed in various clinical trials and their results support the use of this agent in the treatment of severe cases of *Shigella sp.* and *Salmonella sp.* gastroenteritis [59,60]. One of these studies was a prospective, randomized, double-blind, double-dummy trial designed to compare the efficacy and safety of oral ciprofloxacin versus intramuscular ceftriaxone as empiric treatments of acute invasive diarrhea in children [60]. The results of this trial showed no significant differences in the percentage of bacterial eradication rates in the ciprofloxacin-treated patients versus the ceftriaxone-treated group (100% versus 97% respectively for *Shigella sp.*; 73% versus 80% respectively for *Salmonella sp.*; and 71% versus 83%, respectively for *Campylobacter sp.*). Furthermore, clinical cure or improvement was observed in 100% and 99% of the ciprofloxacin versus ceftriaxone groups, respectively.

For enteric *Salmonella sp.* infections, beta-lactam antibiotics are usually indicated however, clinical failures are

frequent and patients usually require the use of second-line agents [61, 62]. The activity of pefloxacin against *Salmonella sp.* infections was studied in a small pilot study that included 16 children ages 1 month to 9.5 years of age with severe *Salmonella sp.* infections that were treated with conventional antibiotics. In this study, 7 / 16 patients had a clinical failure to conventional antimicrobial therapy and pefloxacin was administered achieving complete resolution of symptoms within 1-3 days in all 7 children [63].

A latter study analyzed the efficacy of ciprofloxacin against patients with severe salmonellosis [64]. In this study, 98 children between the ages of 1 month to 15 years of age, with positive blood or stool cultures for *Salmonella sp.*, were treated initially with conventional antibiotics (ceftriaxone in 93 cases). Seventy two of 98 (73%) patients responded promptly; however, despite good in-vitro activity 26/93 (27%) of the ceftriaxone treated patients failed treatment and were treated with oral ciprofloxacin achieving clinical success in a 100% of the cases. Further analysis, of post-therapy asymptomatic *Salmonella* carriage, showed carriage rates of 58% in the ceftriaxone group versus 23% in the ciprofloxacin group.

Typhoid fever is also often treated with beta-lactam antimicrobials particularly ceftriaxone [61,62]. Due to the poor penetration into infected cells, beta-lactam antibiotics are ineffective in approximately 10% of the cases. A small trial in children done by Dutta *et al.* studied the efficacy of ciprofloxacin in cases of multiresistant *Salmonella typhi* and demonstrated bacteriologic and clinical success rates of 96% (17 of 18 patients cured) [59]. Wallace *et al.* in a randomized trial comparing the efficacy of ciprofloxacin versus ceftriaxone in the treatment of blood culture positive typhoid fever demonstrated a clinical failure rate of 27% in patients treated with ceftriaxone compared to 0% in the ciprofloxacin group [65]. Furthermore, the 6 patients that failed therapy to ceftriaxone were treated with ciprofloxacin and clinical resolution was achieved in all of them. In this study, patients with ceftriaxone resistant strains of *Salmonella typhi* and those with susceptible strains responded equally well to ciprofloxacin therapy.

Resistance trends in pediatric enteric pathogens have shown an increased resistance to commonly used antibiotics including ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. Ciprofloxacin and ceftriaxone appear to be very active *in-vitro* with almost no resistance among *Shigella sp.* and *Salmonella sp.* species and a 6% ciprofloxacin-resistance rate among *E. coli* [60]. Exceptionally, in-vitro studies of *Campylobacter sp.* have shown an increase in fluoroquinolone resistance from 0% in 1980 to 12 to 29% in 1998 and 12 to 30% in 2001 [66].

Fluoroquinolones appear to be effective alternatives in the treatment of gastrointestinal infections. Treatment of *Shigella sp.* infections with oral ciprofloxacin is equally effective as intramuscular ceftriaxone and potentially, is an effective alternative when beta-lactam antibiotics fail to treat patients with *Salmonella sp.* infections. Reports of emerging fluoroquinolone resistance, mainly in *Campylobacter* species, suggest a unique use of these antibiotics in patients with severe gastrointestinal infections.

COMPLICATED URINARY TRACT INFECTIONS

In December 2003 the F.D.A. approved the use of ciprofloxacin in children for the treatment of complicated urinary tract infections due to *Escherichia coli* [67]. The approval was based on the results of a pivotal clinical trial that demonstrated similar bacteriological eradication rates and end-of-treatment clinical success when oral or intravenous ciprofloxacin was compared against standard antimicrobial therapy.

The safety analysis of these trials showed an incidence of arthropathy, at a 6 week follow-up, of 9.3% in the ciprofloxacin group versus 6% in the comparator group. All joint events occurring at 6 weeks resolved within 30 days after treatment and at a one year follow-up rates of arthropathy were 13.7% and 9.5% for the ciprofloxacin versus the control group, respectively. The investigators assessment was that none of the cases were related to the study drug.

OTHER INFECTIONS

Effective treatment of *Streptococcus pneumoniae* has been a major goal in pediatric infectious disease and the concern has grown after the introduction of the *Haemophilus influenzae* type B vaccine and by an increasing rate of resistance to commonly used antibiotics [68,69]. The newer fluoroquinolones, particularly gatifloxacin and trovafloxacin, are highly active against *Streptococcus pneumoniae* even in cases of penicillin or cephalosporin resistance [14,15,70,71]. The antimicrobial activity and pharmacologic behavior of some fluoroquinolones, has promoted clinical trials studying their efficacy in the treatment of children with bacterial meningitis and upper respiratory infections, particularly recurrent otitis media and treatment failure otitis media [72-83].

BACTERIAL MENINGITIS

The value of quinolones in the treatment of children with bacterial meningitis was studied by Sáez-Llorens *et al.* who recently conducted a prospective, multicenter, randomized, double-blind clinical trial comparing the safety and efficacy of trovafloxacin with that of ceftriaxone with or without vancomycin [74]. The results of this trial showed no significant differences between trovafloxacin and the comparator group either in clinical success (79% versus 81%, respectively), bacteriologic eradication (94% versus 96%, respectively), mortality (2% versus 3%, respectively), incidence of seizures after enrollment (22% versus 21%, respectively) or short or long term (6 – 12 months post therapy) joint abnormalities (<1% versus 2%, respectively). Although trovafloxacin was withdrawn from the market due to associated liver toxicity, this study was able to demonstrate therapeutic equivalence between this quinolone and a third generation cephalosporin with or without vancomycin for the treatment of bacterial meningitis, a fact that suggests that other fluoroquinolones might play a role in pediatric bacterial meningitis [75].

The efficacy of fluoroquinolones in the chemoprophylaxis of *Neisseria meningitidis* infections has also been studied and available data suggest that a single dose of 400 mg of ofloxacin, in tonsillopharyngeal carriers of *Neisseria*

meningitidis, was effective (97.2%) in eradicating carriage on *N. meningitidis* for a period of 33 days, with no case of meningococcal disease occurring after 6 months [76]. Other studies compared the efficacy of ciprofloxacin versus that of rifampin or ceftriaxone in eradicating *Neisseria meningitidis*, showing equal rates of nasopharyngeal eradication (91.1%, 97.7% and 97.6%, respectively) with no differences in side effects [77].

OTITIS MEDIA

The management of recurrent otitis media and otitis media treatment failure is becoming more difficult due to increased resistance of *Streptococcus pneumoniae* and other otitis media pathogens to penicillin, macrolides and cephalosporins. The only F.D.A. approved antibiotic for treatment of recurrent otitis media is high dose amoxicillin/clavulanate [78]. The newer fluoroquinolones have excellent penetration into the middle ear fluid (MEF) and their efficacy has been assessed in various clinical trials demonstrating good clinical and bacteriological efficacy [78-83]. Two of these studies were phase 3 randomized investigator blinded, multicenter, comparative studies of gatifloxacin versus amoxicillin/clavulanate for the treatment of recurrent otitis media and otitis media treatment failure [81,82]. In one study, high dose amoxicillin/clavulanate (90 mg/kg/day) was used as the comparator and in the other, regular dose amoxicillin/clavulanate (45 mg/kg/day) was the comparator. In the two studies the end-of-therapy and end-of-study clinical cures were similar between gatifloxacin and the two amoxicillin/clavulanate regimens. Furthermore, in both studies adverse event rates were similar and joint related events were limited to transient mild to moderate arthralgias in 2.2% of patients with gatifloxacin versus 1.5% in patients receiving amoxicillin/clavulanate.

Another open label, double tympanocentesis, clinical trial assessed the clinical success and bacteriological eradication rates of levofloxacin against otitis media pathogens in children with otitis media in whom a baseline tympanocentesis was followed by a during-treatment tympanocentesis 3-5 days after starting levofloxacin therapy [83]. In this study a total of 204 patients were enrolled and among 92 microbiologically evaluable children, bacteria were eradicated from the MEF in 82 (89%) with an overall end-of-treatment clinical success of 93.8%. A 100% during-treatment eradication rate among children with baseline *H. influenzae* was documented, an important finding because of the high prevalence of this pathogen in this specific patient population.

Concerns have been expressed about the overuse of fluoroquinolones in children with otitis media and the potential emergence of fluoroquinolone-resistant *S. pneumoniae* strains [84]. Emergence of resistance is theoretically more likely in children, because they carry *S. pneumoniae* strains in their nasopharynx for longer periods of time and with a higher inoculum size than adults. Although this concern is not quinolone-specific and should apply to all the antimicrobial families, it should be acknowledged that resistance to gatifloxacin requires mutations in two different target proteins, which is clearly less likely to occur than mutations leading to resistance in

other antibiotics, such as penicillins or macrolides [85]. Moreover *in vitro* experiments have shown that selection of quinolone-resistant strains of *S. pneumoniae* occurs less frequently with the 8-methoxyfluoroquinolones gatifloxacin and moxifloxacin than with other fluoroquinolones, such as ciprofloxacin and levofloxacin [86,87].

Safety of Fluoroquinolones in Children

Concerns of arthrotoxicity have limited the use of fluoroquinolones in children [1, 2], however, multiple controlled prospective and retrospective studies have demonstrated that the incidence of adverse events of fluoroquinolones is comparable to other antimicrobials and that bone or joint cartilage toxicity is an animal specific issue not affecting humans [88]. Similar to most antibiotics, the most common side effect of fluoroquinolones is gastrointestinal disturbance, followed by central nervous system effects and skin changes [89-91]. Other less frequently side effects, observed mainly in adults included phototoxicity associated with the use of sparfloxacin; cardiotoxicity in patients treated with grepafloxacin, and central nervous system reactions (mainly dizziness) and severe liver toxicity observed with trovafloxacin [92-94] (Table 2).

The longer adverse effects experience with the use of fluoroquinolones in pediatrics has been collected in children receiving ciprofloxacin therapy [67,68,89]. The safety data collected with this agent indicate that the rate of drug related adverse events in children using ciprofloxacin is low (12%) with gastrointestinal side effects being the most frequently reported event followed by headache and abdominal pain. Other less frequently reported side effects are: hypersensitivity reactions, injection site reactions, musculoskeletal events and psychiatric disorders with the vast majority of these being mild and reversible.

The widespread use of ciprofloxacin in children on a compassionate basis, has allowed the creation of large

databases to assess potential arthrotoxicity. In one of the largest reported series [90], more than 1,700 children treated with ciprofloxacin for an acute illness, were retrospectively reviewed failing to demonstrate any joint-related adverse events at 45 days after treatment. Prospective studies evaluating the use of ciprofloxacin in CF children have also not been able to demonstrate an increase in incidence of adverse musculoskeletal events documented either by magnetic resonance imaging [95] or by histological studies [25,96]. A recent study, followed ciprofloxacin treated neonates for the appearance of adverse events during one year, finding no clinical arthropathy or growth impairment [97].

More recently, a retrospective observational cohort study, analyzed the incidence of joint disorders of selected fluoroquinolones and compared the incidence against that observed with azithromycin, a drug with no known effect on tendon or cartilage in humans or animals [89]. This study involved more than 6,000 azithromycin treated children and approximately 20,000 fluoroquinolone treated children younger than 18 years. The objective of this study was to identify the incidence of potential tendon or joint disorders at 60 days post-treatment by a blinded medical record reviewer. The results showed an incidence of joint disorders of 0.82% for ofloxacin and ciprofloxacin treated children versus a 0.78% those children treated with azithromycin. When compared to azithromycin, relative risks of joint disorders were 1.04 [95% Confidence Interval (95% CI) 0.72 to 1.51] for ciprofloxacin and 1.04 (95% CI 0.55 to 1.81) for ofloxacin. Furthermore, a recent prospective study that analyzed the long term safety (12 months) of gatifloxacin in children also failed to demonstrate any quinolone associated arthropathy [98,99].

The current retrospective and prospective published data indicate that the incidence of fluoroquinolone adverse events is similar to other antimicrobials and that some of these side

Table 2. Fluoroquinolone Related Adverse Events [89,92]

Quinolone	Gastrointestinal tract	Central Nervous System	Musculoskeletal	Serious Adverse Events
Nalidixic Acid	< 1%	2-5%	NR ¹	NR
Ciprofloxacin	15%	3%	13%	NR
Levofloxacin	2-6%	NR	5%	NR
Sparfloxacin	10-12%	NR	NR	Phototoxicity ²
Grepafloxacin	3-10%	2-3%	NR	QT interval prolongation ²
Temafloxacin	-	-	-	Renal Failure, Hemolysis ²
Gatifloxacin	NR	NR	NR	NR
Trovafloxacin	6%	4%	NR	Liver toxicity ²
Moxifloxacin	9-12%	NR	NR	NR
Gemifloxacin	7%	<1%	NR	NR

¹ NR = None.

² Withdrawn from the market due to serious adverse.

effects might be specific to certain quinolones. Studies in children have found no increased risk of arthrototoxicity associated with fluoroquinolones and furthermore, when arthralgia was documented it was mild and transient and no permanent damage was observed. The current data indicates that the musculoskeletal toxicity observed in selected animal models is a theoretical concern rather than a real issue, suggesting that the use of fluoroquinolones should not represent an increased risk for side-effects among the pediatric population.

CONCLUSIONS

Clinical trials have documented that fluoroquinolones are safe in pediatrics and that clinical outcomes, in different diseases of children, are similar or better than the outcomes observed with standard therapy. The in-vitro activity of these compounds against multiple antimicrobial resistant pathogens offers a needed therapeutic alternative for these pediatric patients. Based on current information it is expected that quinolones are approved for the treatment of the specific diseases discussed in the current review. Recommendations on the use of fluoroquinolones in children suggest that these agents must remain a therapeutic alternative in selected pediatric conditions.

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