Clinical Use of Fluoroquinolones in Children

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OBJECTIVE: To review the pharmacokinetics, efficacy, and safety of fluoroquinolones in children.

DATA SOURCES: A MEDLINE search (January 1966–March 1998) was conducted for relevant literature.

STUDY SELECTION AND DATA EXTRACTION: Data from compassionate use and published studies were reviewed for the assessment of pharmacokinetics, efficacy, and safety of fluoroquinolones in children.

DATA SYNTHESIS: Fluoroquinolones have a broad spectrum coverage of gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and intracellular organisms. Fluoroquinolones are well absorbed from the gastrointestinal tract, have excellent tissue penetration, low protein binding, and long elimination half-lives. These antibiotics are effective in treating various infections and are well tolerated in adults. However, the use of fluoroquinolones in children has been restricted due to potential cartilage damage that occurred in research with immature animals. Fluoroquinolones have been used in children on a compassionate basis. Ciprofloxacin is the most frequently used fluoroquinolone in children, most often in the treatment of pulmonary infection in cystic fibrosis as well as salmonellosis and shigellosis. Other uses include chronic suppurative otitis media, meningitis, septicemia, and urinary tract infection. Safety data of fluoroquinolones in children appear to be similar to those in adults. Fluoroquinolones are associated with tendinitis and reversible arthralgia in adults and children. However, direct association between fluoroquinolones and arthropathy remains uncertain.

CONCLUSIONS: Fluoroquinolones have been found to be effective in treating certain infections in children. Additional research is needed to define the optimal dosage regimens in pediatric patients. Although fluoroquinolones appear to be well tolerated, further investigations are needed to determine the risk of arthropathy in children. However, their use in children should not be withheld when the benefits outweigh the risks.

KEY WORDS: fluoroquinolones, pediatrics.

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In the early 1960s, nalidixic acid was the first quinolone introduced into clinical practice.[1] Numerous modifications of nalidixic acid have been made to improve antimicrobial, pharmacokinetic, and therapeutic properties. Fluoroquinolones developed subsequently have increased bactericidal effect and activity against a wide spectrum of gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and intracellular organisms.[2,3] Additionally, most of these agents are well absorbed from the gastrointestinal tract, have excellent tissue penetration, low protein binding, and long elimination half-lives.[4-6] Some of the recently marketed quinolones have an expanded activity against gram-positive organisms (e.g., *Streptococcus pneumoniae, Staphylococcus aureus*, enterococci) and anaerobes that are resistant to ciprofloxacin and ofloxacin.[7-11]

Fluoroquinolones have been studied extensively in adult populations and have been found to be well tolerated and effective in the treatment of various infections.[3,12-16] However, their use in children younger than 18 years of age has been limited. The restriction for quinolones in children and adolescents is based on their potential to cause cartilage toxicity in weight-bearing joints in immature animals. Quinolones have been used in millions of pediatric patients, despite lack of their approval by the Food and Drug Administration (FDA) for use in infants and children. This article describes the pharmacokinetics, efficacy, and safety of fluoroquinolones in children.

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Pharmacokinetic Studies

Fluoroquinolone pharmacokinetic data in children are limited as a consequence of their restricted use. Appendix I

shows our experience with ciprofloxacin formulation (unpublished data). The pharmacokinetics of ciprofloxacin were studied in 16 children (7 infants, age 5–14 wk; 9 children, age 1–5 y) after administration of a single oral dose (15 mg/kg) on an empty stomach.[17] The oral mixture was prepared by grinding the tablet and mixing it with 50 mL of water. Timed serum samples were taken during 12 hours after administration of the drug. The mean ± SD peak concentration (C_{max}) values in infants and children were 3.3 ± 1.3 and 2.1 ± 1.4 mg/L, respectively; time to reach C_{max} (t_{max}) was 1.18 ± 0.46 and 1.0 ± 0.25 hours, respectively. There were no differences in the C_{max} or t_{max} between the groups. The $AUC_{0-\infty}$ was greater ($p < 0.01$) in infants than in children (16.1 ± 7.4 vs. 5.3 ± 3.3 mg•h/L, respectively). The elimination half-life of ciprofloxacin was longer ($p < 0.001$) in infants than in children (2.73 ± 0.28 vs. 1.28 ± 0.52 h, respectively). Ciprofloxacin elimination half-life in children seems to be shorter than in adults (3–5 h). The authors suggested increasing the frequency of oral ciprofloxacin to three times daily in children aged one to five years.

The pharmacokinetics of oral and intravenous ofloxacin have been studied[18] in 17 children (age 5–14 y) with typhoid fever. The patients were randomized to receive ofloxacin 7.5 mg/kg orally followed by 7.5 mg/kg intravenously over 30 minutes (7 pts) or the same dose intravenously and then orally (10 pts). The mean oral bioavailability was 91%, which is similar to that for healthy adult volunteers. The mean C_{max} of ofloxacin was significantly higher ($p = 0.0008$) after a single intravenous dose (8.7 mg/L) compared with a single oral dose (5.5 mg/L). Following single intravenous and oral doses, the $AUC_{0-\infty}$ values were 34.13 and 32.32 mg•h/L, respectively. The mean t_{max} values following single intravenous and oral doses were 0.5 and 1.69 hours, respectively. The mean apparent volume of distribution after intravenous administration was 1.28 L/kg. The order of the route of administration (iv first or po first) had no significant effect on the C_{max}, t_{max}, or AUC.

The pharmacokinetic properties of ciprofloxacin in children with cystic fibrosis have been evaluated in two studies. In the first study,[19] 10 children with cystic fibrosis (age 6–16 y) received two intravenous infusions of ciprofloxacin 10 mg/kg every 12 hours, followed by oral administration of 15 mg/kg every 12 hours. Timed blood samples were taken after each infusion and after the first oral dose. Mean C_{max} values were 8.5 and 8.3 mg/L after first and second intravenous infusions, respectively, and 3.5 mg/L after oral dose. The binding of ciprofloxacin to plasma proteins was approximately 34%, similar to that in adults. Body weight was correlated linearly with the total body clearance (clearance L/h = 8.8 + 0.396•weight in kg). There was no correlation between other pharmacokinetic parameters and weight or age. The suggested dosage regimens for treatment of cystic fibrosis with ciprofloxacin were 20–28 mg/kg orally twice daily for younger children (body weight 14–28 kg) and 15–20 mg/kg orally twice daily for older children (body weight 29–42 kg). The suggested intravenous dose was 10–15 mg/kg twice daily for all children.

In another study,[20] the pharmacokinetic properties of sequential intravenous/oral ciprofloxacin were studied in children with cystic fibrosis. Eighteen children (age 5–17 y) were given intravenous ciprofloxacin 10 mg/kg every eight hours and 20 mg/kg orally every 12 hours. The mean steady-state C_{max} values after intravenous infusion and oral doses were 5.0 ± 1.5 and 3.7 ± 1.4 mg/L, respectively; t_{max} was 2.5 ± 1.8 hours following oral doses. The mean oral bioavailability of ciprofloxacin in younger children was less than that in older children (68% vs. 95%, respectively); mean oral bioavailability in adults was 75%. The mean half-life ranged from 2.6 to 3.4 hours. The authors recommended higher doses of ciprofloxacin (30 mg/kg/d iv and 40 mg/kg/d po) in patients with cystic fibrosis.

The pharmacokinetics of trovafloxacin were studied in infants and children.[21] Six infants (age 3–12 mo) and 14 children (1.7–12.5 y) were given intravenous alatrofloxacin (the iv prodrug of trovafloxacin) 4 mg/kg as a single dose. In children, the mean ± SD total clearance, volume of distribution, and elimination half-life were 0.135 ± 0.07 L/h/kg, 1.74 ± 0.89 L/kg, and 9.42 ± 3.52 hours, respectively; the corresponding values in infants were 0.158 ± 0.07 L/h/kg, 1.72 ± 0.67 L/kg, and 8.25 ± 3.7 hours, respectively. The pharmacokinetics in infants and children were similar ($p > 0.05$). In another study,[22] alatrofloxacin 180 mg/m² was given to 27 children (age 1–12 y). The mean C_{max}, clearance, volume of distribution, and half-life were 6.75 mg/L, 0.127 L/h/kg, 2.54 L/kg, and 10.9 hours, respectively. Eleven children (3–12 mo) also received intravenous alatrofloxacin 5 mg/kg once daily. Following the 5-mg/kg doses, the cerebrospinal fluid (CSF) concentrations were 0.93, 1.51, 0.58, 0.49, and 0.39 mg/L, respectively, at 1, 2.6, 3.1, 6.1, and 12 hours after start of infusion. The pharmacokinetics of trovafloxacin in this study were similar to those in adults.

Efficacy

Efficacy data on fluoroquinolones in children are available from their compassionate use and from a few clinical studies. These agents have been used in children mainly in the treatment of pulmonary infections in cystic fibrosis and to treat endemic and epidemic shigellosis and salmonellosis in developing countries. Other uses include chronic suppurative otitis media, meningitis, prevention of meningitis in nasopharyngeal carriers of *Neisseria meningitidis*, shunt infections of the central nervous system, complicated urinary tract infections, and multidrug-resistant tuberculosis. The frequently used doses of some fluoroquinolones in children appear in Table 1.

CYSTIC FIBROSIS

Bronchopulmonary infection with *P. aeruginosa* and *S. aureus* is a major cause of morbidity and mortality in cys-

tic fibrosis.[23] *P. aeruginosa* becomes the predominant pulmonary pathogen with time.[23-25] Complete eradication of chronic *P. aeruginosa* is not achievable. However, there is no clear correlation between clinical improvement and bacteriologic eradication. Antibiotic therapy has been shown to be a major factor in improving survival in patients with cystic fibrosis.[26] Combination parenteral therapy with an aminoglycoside and an antipseudomonal β-lactam is the standard treatment for acute pulmonary exacerbation. However, parenteral therapy often requires hospitalization, and relapse after treatment may necessitate maintenance therapy. Because of its good activity against *P. aeruginosa* and good oral bioavailability, ciprofloxacin has been used in the treatment of pulmonary infection in some adults with cystic fibrosis.[27-31] Ciprofloxacin is the most extensively studied fluoroquinolone in patients with cystic fibrosis. It has been used for treatment of acute exacerbation of pulmonary infections and for maintenance therapy. Several studies of ciprofloxacin in children with cystic fibrosis have been published (Table 2).[32-35]

Ciprofloxacin as monotherapy has been shown to be as effective as the standard combination therapy in pediatric patients.[30,31,34,35] However, a major concern of using ciprofloxacin alone in patients with cystic fibrosis is the emergence of resistance.[31] This is particularly an issue when prolonged maintenance or prophylactic therapy is used. To reduce the risk of resistance, intravenous fluoroquinolones should be reserved for the treatment of acute exacerbation when standard therapy has failed or could not be used due to microbial resistance or adverse effects. Oral fluoroquinolones should be reserved for outpatient treatment of documented *P. aeruginosa* infection in symptomatic patients or for short maintenance therapy after initial intravenous therapy; they should not be used for prophylaxis. Inhaled aerosolized antibiotics (e.g., aminoglycosides, col-

Table 1. Frequently Used Doses of Fluoroquinolones in Children[a]

Drug	Route	Dose[b] (mg/kg)	Frequency
Ciprofloxacin	oral	15	q12h
	iv	10	q12h
Norfloxacin	oral	5–7.5	q12h
Ofloxacin	oral	7.5	q12h
	iv	7.5	q12h
Pefloxacin	oral	10	q12h
	iv	10	q12h
Trovafloxacin	oral	3	q24h
	iv	4–5	q24h

[a]The dosage regimens are based on limited data in children.
[b]Patients with cystic fibrosis may require higher doses, for example, ciprofloxacin dose may be 20 mg/kg po and 15 mg/kg/iv q12h.

Table 2. Clinical Efficacy Studies of Ciprofloxacin in the Treatment of Children with Cystic Fibrosis

Reference	Study Design	No. Pts.	Age (y)	Regimen	Clinical Outcome	Bacterial Eradication	Comments
Rubio (1990)[32]	unknown	24 (39 courses)	2.7–16	CIP 20 mg/kg q12h po for 21–76 d	100% improved in symptoms	eradication not achieved in any patient	median MIC increased from 0.03 to 0.13 mg/L at end of therapy
Schaad et al. (1997)[33]	P,R,O,C	21	4–25 (62% <15)	CIP 30 mg/kg/d q12h po for 3 mo	20 improved in symptoms, 1 had failure	26% eradication; 74% recurrence of *P. aeruginosa* at end of 3 mo	pts. received 2 wk of iv CTZ and AMK before maintenance therapy; iv therapy resulted in a negative culture in 90% and 65% with CIP and CIP/inhalation groups, respectively
		23	5–26 (65% <15)	CIP 30 mg/kg/d q12h po + AMK 500 mg inhalation q12h for 3 mo	20 improved in symptoms; 3 had failure	53% eradication; 47% recurrence of *P. aeruginosa* at end of 3 mo	
Church et al. (1997)[34]	P,R,DB,C, MC	41	5–17	CIP 10 mg/kg q8h iv for 7 d; then CIP 20 mg/kg q12h po for 3 d	100% improved at end of therapy; 3 failures by 2–4 wk	29% eradication rate at end of therapy	clinical improvement defined as no need for additional anti-pseudomonal therapy
		43	6–17	CTZ 50 mg/kg q8h iv + TOB 3 mg/kg q8h iv for 10 d	100% improved at end of therapy; 2 failures by 2–4 wk	53% eradication rate at end of therapy	
Richard et al. (1997)[35]	P,R,O,C, MC	55	5–17	CIP 15 mg/kg q12h po for 2 wk	93% improved	26.4% eradication rate	clinical improvement was reduction in severity and/or number of signs and symptoms, no additional anti-microbial therapy needed
		53	5–17	CTZ 50 mg/kg q8h iv + TOB 3 mg/kg q8h iv for 2 wk	96% improved	69.5% eradication rate	

AMK = amikacin; C = comparative; CIP = ciprofloxacin; CTZ = ceftazidime; DB = double blind; MC = multicenter; MIC = minimum inhibitory concentration; O = open; P = prospective; *P. aeruginosa* = *Pseudomonas aeruginosa*; R = randomized; TOB = tobramycin.

istin) have been used as prophylaxis to prevent chronic infection in patients with cystic fibrosis. This method has been developed to optimize delivery of antimicrobial agents at the site of infection and to reduce systemic toxicity.[36]

SALMONELLOSIS/SHIGELLOSIS

Salmonellosis is a major health problem in developing countries, causing severe morbidity and mortality. It is an endemic disease in Africa, Southeast Asia, the Indian subcontinent, and South and Central America.[37,38] The emergence of multidrug-resistant Salmonella (MDRS) has further complicated the problem. Since 1987, outbreaks of MDRS (resistant to ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole) have been reported in many developing countries.[38,39] Resistant strains have also been isolated in developed countries, primarily among international travelers.[38,40-42] Children, particularly infants, are at higher risk of morbidity and mortality from infection with MDRS.[38,43]

Therapeutic options for MDRS include third-generation cephalosporins[44-46] and fluoroquinolones.[47-51] Third-generation cephalosporins are approved for use in children and have an excellent safety profile; however, they are expensive and must be given parenterally. Therapeutic failure and relapse in MDRS have occurred with cephalosporins, even when active in vitro.[48,52] Third-generation cephalosporins were associated with relapse, failure, and death in patients with Salmonella meningitis.[53,54] In two comparative studies, ceftriaxone was less effective than ciprofloxacin[55] and ofloxacin[56] in the treatment of typhoid fever. Clinical response to cefotaxime was less favorable than that to ofloxacin.[57] In addition, duration of fever was shorter with fluoroquinolones than with cephalosporins.[55,58,59]

Fluoroquinolones possess unique properties for treating various gastrointestinal infections. One advantage is that the gastrointestinal absorption of fluoroquinolones is not affected by diarrhea.[60] In addition, high concentrations of fluoroquinolones in the intestinal lumen are maintained for several days.[61] Salmonella strains resistant to fluoroquinolones have rarely been reported.[62,63] Several studies[49-51,57,64-71] have demonstrated the efficacy and safety of fluoroquinolones in children with Salmonella infection. These are summarized in Table 3.

Shigellosis is another gastrointestinal infection causing morbidity and mortality among young children in the developing world.[72] Antibiotics used for treating shigellosis include ampicillin, tetracyclines, and trimethoprim/sulfamethoxazole; however, the widespread emergence of resistant strains limits the use of these agents.[69,72] Nalidixic acid–resistant strains have emerged in some areas.[73-75] Fluoroquinolones have been shown to be highly effective in vitro against Shigella spp.[76,77] In adults, norfloxacin given as a single dose was as effective as five days of treatment with trimethoprim/sulfamethoxazole.[78] The efficacy data of fluoroquinolones in children with shigellosis are shown in Table 3.

CHRONIC SUPPURATIVE OTITIS MEDIA

Chronic suppurative otitis media (CSOM) is characterized by persistent otorrhea through a perforated tympanic membrane or tympanostomy tube for more than six weeks.[79] *P. aeruginosa* is a predominant pathogen. Aminoglycosides and antipseudomonal β-lactam antibiotics are used most often for the treatment of CSOM. An alternative is to use topical aminoglycosides; however, potential ototoxicity has limited the use of these agents.[80] Fluoroquinolones have oral antipseudomonal activity and lack ototoxicity.[81] Use of oral and topical fluoroquinolones may avoid the cost of hospitalization and the inconvenience of parenteral antibiotics. Oral and topical fluoroquinolones have been used effectively in the treatment of CSOM in children.[80,82-84]

The efficacy of oral ciprofloxacin has been studied[82] in children with CSOM, without cholesteatoma, who were infected with *P. aeruginosa* and other gram-negative bacteria. *P. aeruginosa* was isolated from 18 children. Twenty-one children between 22 months and 14 years of age (mean 4.33 y) received oral ciprofloxacin 30 mg/kg/d in two divided doses for 14–21 days. Eighteen children (86%) were cured after two to 21 days (mean 9.7) of therapy. Treatment failure occurred in three children who were infected with *P. aeruginosa*. Oral ciprofloxacin was discontinued and intravenous ceftazidime was administered in these patients. Children were assessed during treatment and one year after completion of therapy to determine adverse effects; arthralgia and arthritis did not develop during the study or follow-up period.

The efficacy, systemic absorption, and safety of ciprofloxacin ear drops were evaluated in children with CSOM unresponsive to other therapies.[80] Ten of 11 infected ears were given ciprofloxacin 0.3% ophthalmic solution 3 drops three times daily for 14 days ototopically. By day 7 of treatment, 10 of 11 patients with infected ears were cured (cessation of drainage) or improved (50% reduction in days with drainage, minimal moisture in cavity, or both); these were completely cured by day 14 of treatment. Ciprofloxacin was not detected in the plasma of any child after ototopical instillation. The drug was not associated with adverse effects. Another study[84] evaluated the efficacy and safety of topical ciprofloxacin in children with CSOM unresponsive to other antibiotics. Twenty-nine patients between one and 14 years of age (mean 4.8) with otorrhea and confirmed *P. aeruginosa* were enrolled in the study. Ciprofloxacin was given ototopically as 3 drops of the 0.3% ophthalmic solution three times daily for two weeks. Eighteen of 29 (62%) ears were cured by day 14, and 20 (69%) ears were cured by day 21; the overall improvement rate was 90%. Three patients did not respond, and treatment was switched to other antibiotics. None of the patients reported adverse effects from ciprofloxacin.

Ototopical ciprofloxacin was compared with gentamicin in the treatment of CSOM in children and adults.[83] Forty-four patients between nine and 65 years of age were enrolled in the study. Twenty patients were given 5 drops of gentamicin 5 mg/mL topically three times daily for 10

days. Twenty-four patients were given 5 drops of ciprofloxacin 0.2 mg/mL three times daily for 10 days. In the gentamicin group, six patients (30%) were cured (cessation of the otorrhea and eradication of the microorganism). Twenty-one patients (88%) in the ciprofloxacin group were cured. Three of the patients whose treatment failed had clinical improvement without bacteriologic eradication; *Candida albicans* was isolated from these patients. Clinical efficacy in the ciprofloxacin group was higher than in the gentamicin group ($p < 0.001$). There were no adverse effects, and audiometric evaluation showed no evidence of ototoxicity in either group.

Ofloxacin otic solution has been approved by the FDA for acute otitis media with tympanostomy tubes and otitis externa due to *S. aureus* and *P. aeruginosa* in children one year of age or older, and for CSOM with perforated tympanic membranes in children ≥12 years of age.[85]

TREATMENT AND PROPHYLAXIS OF CENTRAL NERVOUS SYSTEM INFECTIONS

Fluoroquinolones penetrate well into the CSF in the presence of inflamed meninges, and the CSF concentrations exceed the minimum inhibitory concentrations (MICs)

Table 3. Efficacy Studies of Fluoroquinolones in Gastrointestinal Infections in Children

Reference	Type of Infection	No. Pts. (age, y)	Regimen	Clinical Outcome	Comments
Vinh et al. (1996)[51]	uncomplicated MDR typhoid fever	53 (2–14) 47 (1–14)	ofloxacin 15 mg/kg/d q12h for 2 d ofloxacin 15 mg/kg/d q12h for 3 d	47 cured without relapse; 6 clinical failures 1 relapse responded to 7-d treatment; 2 clinical failures	clinical response similar in both groups ($p > 0.2$)
Arora et al. (1992)[64]	severe MDR typhoid fever	85 (8 mo–10 y)	ciprofloxacin 20 mg/kg/d q12h for 10 d	all cured; no relapse	6 children had vomiting and received iv treatment for 1–2 d
Bavdekar et al. (1991)[65]	severe MDR typhoid fever	73 (1.5–18)	ciprofloxacin 10 mg/kg/d iv or 20 mg/kg/d po q12h[a]	all cured; no relapse	22% of pts. had life-threatening diseases
Dutta et al. (1993)[49]	severe MDR typhoid fever	18 (1.5–9.5)	ciprofloxacin 10 mg/kg/d q12h iv/po for 7–14 d after being afebrile	17 cured; no relapse	1 child died within 24 h from shock
Gendrel et al. (1993)[50]	severe invasive salmonellosis	7 (1.5–9.5)	pefloxacin 12 mg/kg/d po q12h for 7 d	all cured	1 relapse cured with another 7-d course
Rathore et al. (1996)[66]	MDR typhoid fever	55 (average 6.2)	ofloxacin dose unclear	all cured; no relapse	no long-term follow-up available
Sen et al. (1991)[67]	MDR typhoid fever	8 (2.5–13)	ciprofloxacin 15 mg/kg/d po q12h for 7–10 d	all cured; no relapse at 2-mo follow-up	pts. received ciprofloxacin after failure with other agents
El-Sherbini (1992)[57]	MDR typhoid fever	49 (2–5)	ofloxacin 50–200 mg po q12h for 7 d	96% cured	arthralgia in 4 pts. probably due to typhoid fever
Secmeer et al. (1997)[68]	typhoid fever	24 (<16) 17 (<16)	ofloxacin 20 mg/kg po q12h for 10 d[b] TMP/SMX 10 mg/kg (TMP) q12h for 10 d[b]	improvement by day 4 in all; all cured without relapse improvement by day 4 in 65%; all cured without relapse	ofloxacin produced shorter febrile duration ($p < 0.02$) and faster disappearance of symptoms ($p < 0.0028$) compared with TMP/SMX
Lolekha et al. (1991)[69]	shigellosis	25 (6 mo–13 y) 30 (6 mo–13 y) 24 (6 mo–13 y)	TMP/SMX 6 mg/kg/d (TMP) po q12h for 5 d nalidixic acid 55 mg/kg/d q6h for 5 d norfloxacin 10–15 mg/kg/d po q12h for 5 d	cure rate 100% with nalidixic acid and norfloxacin group; 64% with TMP/SMX ($p < 0.01$)	eradication of *Shigella* was faster with norfloxacin during the first 72 h ($p < 0.01$)
Guyon et al. (1994)[70]	MDR shigellosis MDR shigellosis	25 (8 mo–12 y) 13 (11 mo–13 y)	pefloxacin 12 mg/kg po once daily for 3 d pefloxacin 20 mg/kg po single dose	all cured without relapse all cured without relapse	84% eradication rate at 48 h; 100% at 7 d stool was negative at day 3 and remained negative at days 5 and 8
Bhattacharya et al. (1997)[71]	shigellosis	27 (1–10) 32 (1–10)	nalidixic acid 60 mg/kg/d po q6h for 5 d norfloxacin 20 mg/kg/d q12h for 5 d	cure rate 100% with norfloxacin; 3 pts. in nalidixic acid group failed and responded to norfloxacin	norfloxacin recipients had shorter duration of diarrhea and blood in stool than pts. receiving nalidixic acid ($p < 0.05$)

MDR = multidrug resistant; SMX = sulfamethoxazole; TMP = trimethoprim.
[a]Patients received either ciprofloxacin iv (55%) or po (45%). Ciprofloxacin was given alone in 10% of patients, combined with cefuroxime in 50% of patients, and combined with other agents (i.e., chloramphenicol, amoxicillin, TMP/SMX) in 22%.
[b]Patients received TMP/SMXfor TMP/SMX-susceptible strains, and ofloxacin for TMP/SMX-resistant strains.

for susceptible organisms.[22,86-89] The concentration of fluoroquinolones in the CSF exceeded 50% of the serum concentration in the presence of inflamed meninges.[86] There are case reports in which fluoroquinolones have been used in the treatment of meningitis and ventriculitis in neonates and children.

Two cases of neonatal meningitis were treated successfully with ciprofloxacin.[86] The first involved a two-day-old boy with *Escherichia coli* in the CSF, resistant to ampicillin, gentamicin, chloramphenicol, and trimethoprim, but susceptible to ciprofloxacin and cefotaxime. The patient was treated with ciprofloxacin because cefotaxime was not available in the hospital. Nine doses of intravenous ciprofloxacin 25 mg/kg/d every 12 hours were given; dosage was then switched to 30 mg/kg/d orally every 12 hours for a total of 21 days. The infant slowly improved and was well six weeks later. The second infant was a 13-day-old boy with *Flavobacterium meningosepticum* meningitis; the organism was sensitive only to ciprofloxacin. Intravenous ciprofloxacin 20 mg/kg/d was given every 12 hours for four days; the dosage and schedule were maintained and the drug was given orally for another nine days. The infant responded to ciprofloxacin and recovered without signs of neurologic damage.

Salmonella meningitis in neonates was treated successfully with ciprofloxacin. A six-day-old infant with *Salmonella typhimurium* was treated with chloramphenicol without improvement, despite initial in vitro sensitivity to chloramphenicol.[90] A repeat culture revealed chloramphenicol-resistant *S. typhimurium*; the MIC of ciprofloxacin was 0.006 mg/L. Ciprofloxacin 15 mg/kg/d was given intravenously every 12 hours for 13 days. Blood and CSF specimens were sterile 24 hours after ciprofloxacin was initiated. The patient responded to ciprofloxacin therapy and was discharged on day 29.[88] In another neonate, *Salmonella enteritidis* meningitis was treated successfully with cefotaxime and ciprofloxacin after failure of ceftriaxone and ampicillin.[90]

Pefloxacin was used to treat a neonate with ventriculitis due to *Klebsiella pneumoniae* resistant to penicillins, aminoglycosides, and cephalosporins, and sensitive to imipenem and pefloxacin.[91] Imipenem was given for 23 days, but the infant developed hydrocephalus, and repeat CSF cultures revealed the same organism. Imipenem was discontinued and intravenous pefloxacin was started at 20 mg/kg/d every 12 hours. The patient was afebrile within 24 hours and CSF was sterile within 48 hours. Pefloxacin was continued for 14 days and repeat CSF samples were sterile two and seven days after treatment. In another case,[92] ciprofloxacin was used to treat ventriculitis in a 10-month-old infant. Ceftazidime and amikacin were started after isolation of multiple organisms from the shunt. A repeat culture showed eradication of all organisms except *Enterobacter cloacae*, sensitive to amikacin, imipenem, and ciprofloxacin. After amikacin and imipenem failed to eradicate *E. cloacae*, intravenous ciprofloxacin 35 mg/kg/d every 12 hours was started and continued for 21 days. Cultures were negative on days 5, 12, and 35 after ciprofloxacin therapy was initiated.

A seven-year-old child with head trauma and *Acinetobacter calcoaceticus* meningitis was treated with ceftazidime and ampicillin without improvement.[93] Treatment was then switched to intravenous pefloxacin 300 mg every 12 hours and amikacin 15 mg/kg/d for two weeks. The patient responded rapidly to this treatment and, within 36 hours, was afebrile and CSF culture was negative. The patient remained free of infection but died from cardiac arrest secondary to his underlying condition.

Trovafloxacin was compared with ceftriaxone in the treatment of epidemic meningococcal meningitis in children.[94] Children were randomized to receive trovafloxacin 3 mg/kg orally or intravenously (100 children) or ceftriaxone 100 mg/kg intramuscularly or intravenously (100 children) for five days. CSF cultures were initially positive for *N. meningitidis* in 86% and 81% of patients receiving trovafloxacin and ceftriaxone, respectively. Cure rate was approximately 90% (84/93) with trovafloxacin and 89% (87/97) with ceftriaxone, without relapse at four to six weeks' follow-up for either regimen.

Meningococcal disease is a life-threatening communicable disease causing morbidity and mortality in many parts of the world. Prophylaxis with rifampin, ceftriaxone, and ciprofloxacin in close contacts of patients with meningococcal meningitis is the primary means for prevention of meningococcal disease.[95] A single oral dose of ciprofloxacin has been used successfully in the eradication of nasopharyngeal carriage of *N. meningitidis* in adults.[95,96] Single-dose ciprofloxacin has the advantages of avoiding intramuscular administration of ceftriaxone and the poor compliance associated with multiple days of rifampin therapy.[96] Ciprofloxacin was compared with rifampin for eradication of nasopharyngeal carriage of *N. meningitidis* in children.[97] Ciprofloxacin 15 mg/kg as a single oral dose was given to 469 children (age 2–18 y) of contacts, 79 of whom were documented carriers of *N. meningitidis*. Rifampin 20 mg/kg twice daily for two days was given to 88 carriers. Eradication rates after one and two weeks of treatment were 96.5% and 97.7%, respectively, for rifampin, and 88.6% and 91.1%, respectively, for ciprofloxacin. None of the subjects developed disease in the two weeks following therapy, and none were hospitalized with meningococcal disease over the subsequent year.

OTHER INFECTIONS

In a multicenter, double-blind, randomized, controlled study,[98] the efficacy of ciprofloxacin was compared with that of tobramycin for the treatment of bacterial conjunctivitis in children. A group of 257 children (age <1–12 y) were randomized to receive ciprofloxacin 0.3% or tobramycin 0.3% ophthalmic solutions for seven days. Efficacy was evaluated in 141 patients, 71 in the ciprofloxacin group and 70 in the tobramycin group. Microbial eradication was achieved in 90.1% and 84.3% of patients treated with ciprofloxacin and tobramycin, respectively ($p = 0.29$). Cure

rates after treatment with ciprofloxacin and tobramycin were 87% and 90%, respectively ($p > 0.5$). No serious adverse effects were reported with either regimen.

In Japan, norfloxacin has been studied in the treatment of various infections in children.[99] Norfloxacin had a success rate of 98.1% (104/106) for urinary tract infections, 98.6% (70/71) for Campylobacter enteritis, 95.8% (23/24) for bacillary dysentery, 100% (24/24) for Salmonella enteritis, 100% (6/6) for other enteritis, 81.8% (9/11) for acute pneumonia, and 80.8% (21/26) for other respiratory infections.

Several other reports describe the use of fluoroquinolones in the treatment of various infections. Ciprofloxacin was used in the treatment of septicemia due to multidrug-resistant *E. cloacae* in six neonates; eradication of the bacteria was achieved in all neonates.[100] Endocarditis due to *E. cloacae* and *Haemophilus aphrophilus* was treated successfully with netilmicin and ciprofloxacin in two children.[101] Netilmicin was used for one week in one child and for three weeks in the other child, and oral ciprofloxacin was continued in both children. A five-year-old boy with extrapulmonary multidrug-resistant tuberculosis was treated successfully with kanamycin, cycloserine, and ciprofloxacin.[102] Ciprofloxacin was used for nine months without evidence of adverse effects. Fluoroquinolones have also been used for empiric treatment of febrile neutropenia in pediatric cancer patients.[103]

We have used ciprofloxacin at Children's Hospital in Columbus in the treatment of urinary tract infection due to *P. aeruginosa* as early switch to oral therapy and for prophylaxis. We have also used oral ciprofloxacin in osteomyelitis due to *P. aeruginosa* following the initial patenteral antibiotics.

Safety

The restriction of fluoroquinolone use in children has limited the safety data in this population. Safety data are currently available from the compassionate use of ciprofloxacin. In 1996, more than 8 million prescriptions for ciprofloxacin were written for children <18 years old; 12 000 of these were for infants younger than one year.[104] The most frequent adverse effects of ciprofloxacin reported in >2000 pediatric patients given ciprofloxacin for various indications involved the gastrointestinal tract (4.9%; nausea, vomiting, diarrhea), skin (3.3%; rash, pruritus, urticaria), and central nervous system (2.2%; dizziness, headache, anxiety). The adverse events were mild to moderate in nature and always reversible. Other rare adverse effects included elevation of hepatic aminotransferases (1.7%), arthralgia (1%), and photosensitivity (0.4%).[105,106] Photosensitivity occurs most commonly with agents containing a halogen substituent at the 8-position, such as lomefloxacin and sparfloxacin.[107] In adults, photosensitivity reactions were reported in 10% of patients taking lomefloxacin, 7.9% taking sparfloxacin, and <1% taking ciprofloxacin, ofloxacin, and levofloxacin.[11] It is unclear whether the incidence of photosensitivity would be different in children from that in adults. Following the use of ofloxacin otic solution, the most frequent adverse effects included taste perversion (7%), pruritus (4%), application site reaction (3%), dizziness (1%), earache (1%), and vertigo (1%).[85] The safety profile of ciprofloxacin in children was similar to that in adults.[13-15,105,106]

Arthralgia and arthropathy are the main concerns about the safety of fluoroquinolones in children. To clarify this issue, the musculoskeletal adverse effects of quinolones are discussed in detail.

Musculoskeletal Adverse Effects

Quinolone-induced cartilage toxicity in immature animals has been the basis for nonapproval of the use of fluoroquinolones in children. Arthralgia and tedinopathies have been associated with fluoroquinolones in humans.[108,109] It is unclear whether cartilage toxicity in experimental animals and tendon disorders in humans are related.

CARTILAGE TOXICITY IN ANIMALS

All quinolones may cause cartilage damage when administered to immature animals[110-114]; nalidixic acid was associated with greater arthropathic effect than other quinolones.[110] Arthropathic effects of fluoroquinolones vary among animal species; for example, dogs are the most sensitive species, requiring 30 mg/kg/d of ciprofloxacin to demonstrate cartilage damage, compared with rats, which need 500 mg/kg/d to exhibit the same effect. Mice did not show arthropathy in doses of nalidixic acid as high as 1000 mg/kg/d; dogs developed arthropathy while receiving 100 mg/kg/d. However, quinolone-induced cartilage damage did not appear in an unnamed species of monkey at doses of <500 mg/kg/d.[115] Indeed, the wide variability of animal experience and the fact that humans are different from animals may explain the limited occurrence of quinolone-induced arthropathy in children.

The mechanism of quinolone-associated arthropathy in immature animals is unclear. One hypothesis is that quinolones induce cartilage damage by inhibiting the mitochondrial DNA synthesis in immature chondrocytes; however, this requires further investigation.[116] Another hypothesis is that fluoride may cause direct toxicity to cartilage.[117] However, this is very unlikely since quinolones without fluoride induce cartilage toxicity in experimental animals. In addition, fluorinated agents other than fluoroquinolones do not cause cartilage toxicity. It has been suggested that magnesium deficiency in the cartilage due to chelation with quinolones may cause or aggravate the cartilage damage.[118] Morphologic and histologic findings are characterized by localized blister formation, chondrocyte loss, matrix degeneration, and erosion of the articular cartilage accompanied by a noninflammatory effusion in the cavity of the weight-bearing joints. Chondrocyte necrosis, diffuse dissolution of matrix, and mitochondrial swelling were shown by electron microscopy.[113,119]

MUSCULOSKELETAL EFFECTS IN HUMANS

Tendinopathy

Tendinitis and tendon rupture are adverse effects of fluoroquinolones.[120-127] More than 300 cases of fluoroquinolone-induced tendinitis have been reported in France in a postmarketing spontaneous reporting system.[108] The majority of cases occurred in patients >60 years of age.[125-127] However, this may only reflect the age group of patients likely to use fluoroquinolones. The mechanism of fluoroquinolone-induced tendon disorder remains unclear. The symptoms usually developed as joint pain and swelling followed by difficulty in movement. Rupture of the involved tendons can be a serious complication that may require surgical intervention and cause prolonged disability.[128] The onset of symptoms can occur any time during or after therapy; these may occur within one or two days after starting fluoroquinolone therapy.[125,127,128] Tendinitis usually resolves in a few weeks but may persist over months.[125,126] Concomitant use of corticosteroids was considered a risk factor for tendinitis.[122,125,127,128]

The FDA has asked clinicians to alert patients of the potential for tendinitis and tendon rupture related to quinolone administration. The FDA also sent letters to the manufacturers requesting a revision of the package inserts to include a warning about tendinitis.[129]

Arthropathy and Arthralgia

The potential for arthropathy in children remains uncertain. Bailey et al.[130] were the first to report, in 1972, reversible arthralgia in a woman taking nalidixic acid. Arthralgia and arthropathy have been reported[20,32-35,131,132] in association with fluoroquinolones in adults and children with cystic fibrosis. However, the prevalence of arthropathy is up to 10% in adolescents and adults with cystic fibrosis who were not exposed to quinolones.[133,134] It has been suggested[109] that arthropathy often is not recognized and not reported in cystic fibrosis.

Quinolone-induced arthropathy and arthralgia has been rarely reported in children without cystic fibrosis. The first report[135] was a case of destructive polyarthropathy in a 17-year-old boy after administration of pefloxacin 800 mg/d for three months. The patient initially presented with joint pain and swelling, which deteriorated over three months and resulted in progressive difficulty in walking. X-ray findings showed severe destructive polyarthropathy. Microscopic examination of the cartilage and synovial biopsies revealed fibrosis of the synovial tissue and articular cartilage. Total bilateral knee and right hip replacements were needed. However, there was no baseline X-ray study; thus, preexisting rheumatologic abnormalities may have existed. Arthropathy occurred in a 12-year-old girl treated with oral pefloxacin 400 mg twice daily for typhoid fever.[136] The patient presented with joint pain, fever, and difficulty in rising from bed. The pain did not resolve with nonsteroidal antiinflammatory agents. Pain in all joints resolved over one week after discontinuing pefloxacin, except for left knee pain that lasted for three months. There were no abnormal laboratory or X-ray findings in the joints. The third case[137] involved arthropathy in a 15-year-old patient receiving intravenous pefloxacin 400 mg every 12 hours. Pain, swelling, and redness were noted in six joints. Plain X-ray studies of the right elbow showed no abnormalities, and magnetic resonance imaging (MRI) revealed joint effusion and enhancement of the surrounding muscles and the synovial tissues. Technetium bone scans demonstrated increased initial dynamic perfusion, blood pool at five minutes, and delayed bony uptake at four static images in the right elbow. Pain resolved over two to eight weeks after pefloxacin was discontinued. Ten months later, the MRI was normal; however, technetium bone scans showed persistent abnormalities.

Joint abnormalities were reported[138] in a retrospective, questionnaire-based study of 3341 children with typhoid fever treated with ciprofloxacin during 1990–1994. Arthropathy (joint pain, restriction of movements, swelling of joint) was reported in 20 children (age 2–12 y). Arthralgia developed on days 1–8 of ciprofloxacin therapy and resolved in 18 cases within one day to four weeks of either discontinuing or completing therapy. Outcomes in the remaining two cases were not reported. Joint aspiration was not performed in any child and X-ray findings of the joints were normal in all children. However, the nature of this study and lack of adequate investigation of the articular cartilage did not confirm the relationship between fluoroquinolones and arthropathy. Further, other causes including the underlying disease were not excluded.

Adverse effects to the joints have been evaluated in another study involving children treated with ciprofloxacin.[105] A total of 634 children (age 3 d–17 y) were treated with ciprofloxacin orally or intravenously. The duration of treatment ranged from one to 880 days (mean 22.8). Transient arthralgia was reported in eight girls (1.3%) with cystic fibrosis. Ciprofloxacin was discontinued in three of these patients and arthralgia was then reversed. A comprehensive review[139] of 31 reports on the skeletal safety of quinolones in children has been published. More than 7000 children (age 4 d–18 y) treated with quinolones have been evaluated. The prevalence of arthralgia was no more than that expected from underlying diseases such as cystic fibrosis and salmonellosis. Arthropathy has been associated with up to 10% of patients with cystic fibrosis.[133,134] Reactive arthritis, a nonpurulent arthritis that follows a bacterial infection, has been reported in 7.3% of patients with salmonellosis.[140]

Several studies have been conducted to detect cartilage lesions caused by quinolones using radiologic and MRI evaluations. Twenty-nine children (age 4–18 y) with cystic fibrosis were evaluated for quinolone-induced arthropathy using MRI.[141] Fourteen patients (group 1) were treated with ciprofloxacin or ofloxacin at doses of 20 mg/kg/d for four to 28 days. The remaining 15 patients (group 2) were in a control group, given no quinolones. Transient arthralgia occurred in six patients in group 1 and four patients in

group 2. Seven patients (50%) in group 1 developed changes in the reference joint (left knee) on MRI. In group 2, seven of 10 (70%) had these changes on MRI. The presence of arthrotoxicity could not be confirmed from this study.

In another study,[142] clinical, radiologic, and MRI studies were conducted in 18 pediatric patients with cystic fibrosis treated with ciprofloxacin. The patients were evaluated before and at the end of a three-month treatment with ciprofloxacin and at four to six months' follow-up. There was no evidence of arthropathy at the end of treatment and during follow-up.

Postmortem morphologic studies were performed in two children who died from cystic fibrosis complications.[143] Both children had received ciprofloxacin for nine to 10 months during the last three years of life. Autopsies of the knees, as well as macroscopic, light, and electron microscopic examination showed normal cartilage without evidence of toxicity.

The long-term effect of quinolones on cartilage has been evaluated in children given norfloxacin.[144] Twenty-one children (age 9–12 y) with neutropenia received norfloxacin 20 mg/kg twice daily for one month. No acute or early toxicity occurred. X-ray evaluation of the knee was performed in 17 of the children at a median of 42.7 months (24–62) after treatment. No abnormalities were detected in the radiographic evaluation. Seven years after the initial treatment, five of these patients were evaluated for long-term cartilage damage. MRI was used for evaluation, and results were compared with a control group. All patients had a normal linear growth without evidence of arthropathy.

Nalidixic acid, which is associated with the greater arthropathic effect in immature animals, has been used in children for many years without evidence of cartilage toxicity.[145] In addition, nalidixic acid has been an approved drug for more than three decades for pregnant women and children in many countries.[14,138] Norfloxacin is approved for treatment of urinary tract infection in children in Japan.[146]

To date, safety data of fluoroquinolones in children seem to be similar to those in adults. Fluoroquinolones are associated with tendinitis and reversible arthralgia in adults and children. Arthropathic effects induced by fluoroquinolones in children remain uncertain. The majority of cases with presumed arthropathy were reported with pefloxacin, which is also associated with the highest incidence of tendinitis. It should be noted that there was a lack of consistent definition of arthropathy in the reported cases.

Summary

Fluoroquinolones have been used in children on a compassionate basis, mainly in the treatment of pulmonary infections in cystic fibrosis as well as salmonellosis and shigellosis. Currently, there are few studies on the efficacy of fluoroquinolones in children. Results have suggested that fluoroquinolones were effective in the treatment of various infections in children; however, optimal dosage regimens are unknown. The safety data of fluoroquinolones in children are similar to those in adult populations. The incidence of fluoroquinolone-induced arthropathy in children is not known. Although further research is needed to clearly establish the safety of fluoroquinolones in pediatric patients, the potential therapeutic benefits should be considered in relation to the low probability of debilitating adverse effects. Dosing recommendations for children and oral dosage forms need further development.

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Appendix I. Ciprofloxacin Formulation (50-mg/mL Suspension)[a]

Ingredients	Quantity
Ciprofloxacin	20 500-mg tablets
Ora-Sweet	100 mL
Ora-Plus	100 mL
or	
Simple syrup NF	100 mL
Methylcellulose 1%	100 mL

Instructions

Crush 20 tablets of ciprofloxacin 500 mg in mortar with pestle. Combine 100 mL of Ora-Sweet with 100 mL Ora-Plus, or 100 mL of simple syrup NF with 100 mL of methylcellulose 1%; mix well and add in small amounts to the powder in the mortar while mixing. Transfer this mixture to a graduate and qs to volume. The 50-mg/mL suspension is stable for at least 70 d at both 4 and 25 °C.[a]

[a]Unpublished data.

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EXTRACTO

OBJETIVO: Revisar la farmacocinética, eficacia, y seguridad de las fluoroquinolonas en niños.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de literatura relevante en MEDLINE (enero 1966 a marzo 1998).

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Se revisaron datos de estudios publicados incluyendo referencias de uso compasivo para evaluar la farmacocinética, eficacia, y seguridad de las fluoroquinolonas en niños.

SÍNTESIS: Las fluoroquinolonas tinenen una cubierta de espectro amplio contra bacterias gram-positivo y gram-negativo, incluyendo *Pseudomonas aeruginosa* y organismos intracelulares. Estas se absorben bien del trayecto gastrointestinal, tienen penetración excelente a tejidos, enlace a proteinas bajo y vidas medias de eliminación prolongadas. Estos antibióticos son efectivos tratando varias infecciones y además son bien tolerados en adultos. Sin embargo, el uso de las fluoroquinolonas ha sido restringido en niños debido a daño potencial a cartílagos causado en animales inmaduros. Las fluoroquinolonas han sido utilizadas en niños para uso compasivo. Ciprofloxacina es la fluoroquinolona más frecuentemente usada en niños. La experiencia mayor de su uso en niños ha sido en el tratamiento de infecciones pulmonares en fibrosis cística, salmonelosis, y shigellosis. Otros usos incluyen otitis media crónica supurativa, meningitis, septicemia, e infección del trayecto urinario. Los datos sobre la seguridad de las fluoroquinolonas en niños parecen ser similares a los de los adultos. Las fluoroquinolonas están asociadas a tendinitis y artralgia reversible en adultos y niños. Sin embargo, aún es incierta una asociación directa entre las fluoroquinolonas y el desarrollo de artropatía.

CONCLUSIONES: Se ha encontrado que las fluoroquinolonas son efectivas tratando ciertas infecciones en niños. Se necesitan más investigaciones para definir el régimen de dosificación óptimo en pacientes pediátricos. Aunque las fluoroquinolonas parecen ser bien toleradas, se necesitan también más investigaciones para determinar el riesgo de artropatía en niños. Sin embargo, su uso en niños no se debe evitar cuando los beneficios sobrepasan los riesgos.

JUAN F FELIU

RÉSUMÉ

OBJECTIF: Réviser la pharmacocinétique, l'efficacité, et l'innocuité des fluoroquinolones chez l'enfant.

REVUE DE LITTÉRATURE: Recherche MEDLINE (janvier 1966 à mars 1998).

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les données provenant d'études publiées et de programmes d'utilisation pour fins humanitaires

ont été retenues pour l'évaluation de la pharmacocinétique, de l'efficacité, et de l'innocuité des fluoroquinolones chez l'enfant.

RÉSUMÉ: Les fluoroquinolones ont un large spectre d'activité contre les bactéries gram positif et gram négatif, incluant notamment le *Pseudomonas aeruginosa* et les micro-organismes intracellulaires. Les paramètres pharmacocinétiques révèlent une très bonne absorption au niveau du tube digestif, une excellente pénétration tissulaire, un faible taux de liaison protéique, et une demi-vie d'élimination longue. Ces antibiotiques sont efficaces pour traiter une grande variété d'infections et sont bien tolérés chez l'adulte. Cependant, l'utilisation des fluoroquinolones chez l'enfant est limitée par le risque de dommage au cartilage observé chez les animaux immatures. Les fluoroquinolones ont été utilisées chez l'enfant dans le cadre de programmes d'utilisation pour fins humanitaires. La ciprofloxacine a été la plus fréquemment utilisée chez l'enfant. En pédiatrie, l'expérience porte principalement sur le traitement des infections pulmonaires associées à la fibrose kystique, à la salmonellose, et la shigellose. Les fluoroquinolones ont également été utilisées pour traiter des otites moyennes chroniques, des méningites, des septicémies, ainsi que des infections urinaries. Les données d'innocuité des fluoroquinolones chez l'enfant semblent être similaires à celles de l'adulte. Des cas de tendinite et d'arthralgies réversibles ont été notés chez l'enfant et chez l'adulte. Cependant, une association directe entre les fluoroquinolones et l'arthropathie demeure incertaine.

CONCLUSIONS: Les fluoroquinolones sont efficaces pour traiter certaines infections en pédiatrie. Des données supplémentaires devront être obtenues afin de préciser les doses optimales chez l'enfant. Bien qu'elles semblent être bien tolérées, les fluoroquinolones devront faire l'objet d'études additionnelles dans le but de déterminer le risque d'arthropathie chez l'enfant. Leur utilisation chez l'enfant devrait tout de même être considérée, notamment lorsque les bénéfices dépassent les risques.

ALAIN MARCOTTE