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Systemic use of fluoroquinolone in children

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Fluoroquinolones are an important class of antibiotics that are widely used in adult patients because of their broad spectrum of activity, good tissue penetration, and oral bioavailability. However, fluoroquinolone use in children is limited because juvenile animals developed arthropathy in previous experiments on fluoroquinolone use. Indications for fluoroquinolone use in patients younger than 18 years, as stated by the U.S. Food and Drug Administration, include treatment of complicated urinary tract infections and postexposure treatment for inhalation anthrax. In Korea, the systemic use of fluoroquinolones has not been approved in children younger than 18 years. Although concerns remain regarding the adverse musculoskeletal effects of fluoroquinolones in children, their use in the pediatric population has increased in many circumstances. While pediatricians should be aware of the indications and adverse effects of fluoroquinolones, recent studies have shown that the risk for musculoskeletal complications in children did not significantly increase following fluoroquinolone treatment. In addition, fluoroquinolones may be particularly helpful in treating multidrug-resistant infections that have not responded to standard antibiotic therapy in immunocompromised patients. In the present article, we provide an updated review on the safety and current recommendations for using fluoroquinolones in children.

Key words: Fluoroquinolones, Adverse effects, Joint diseases, Child

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Introduction

Fluoroquinolones (FQs) are important antibiotics that are widely utilized in adult patients because of their excellent spectrum of activity, good tissue penetration, and oral bioavailability. FQ use in children remains limited because of arthropathy observed in juvenile animals[1-5]. However, several reports have described using FQs to treat serious infections in children despite their few approved indications[6-12]. In the present article, we reviewed the data, particularly from the last ten years, focusing on the current recommendations for the use and safety profile of FQs in children.

Overview of FQs

1. Classification

Nalidixic acid, a first generation FQ, was initially introduced in 1964 for the treatment of urinary tract infections, and for more than 2 decades, it was used in children 3 months and older without restriction[2-4]. Nalidixic acid was discovered accidentally by Lesher and coworkers as a by-product of the synthesis of the antimalarial compound

chloroquine[4]. This discovery led to the development of quinolone compounds, and fluorination of quinolone led to the introduction of second-generation of FQs like norfloxacin in 1986 and ciprofloxacin in 1987. Other second-generation FQs, like levofloxacin, followed soon thereafter. The addition of the fluorine atom improves potency, enhances antimicrobial activity, and alters pharmacokinetic properties. Incorporating different substituents to various positions on the quinolone nucleus varies antimicrobial activity and alters FQ side-effect profiles[3,4,13]. Currently, there are 4 generations of FQ antibiotics; among these, ciprofloxacin, levofloxacin, and moxifloxacin represent the most widely used systemic FQs (Fig. 1).

2. Clinical pharmacology

FQs are bactericidal and inhibit bacterial DNA synthesis by interfering with DNA gyrase and topoisomerase IV, both of which are necessary for DNA replication. FQs have advantageous pharmacokinetic properties such as gastrointestinal absorption (bioavailability of 70–95%), excellent penetration into many tissues, and good intracellular diffusion. Peak plasma concentrations of levofloxacin and moxifloxacin are generally attained within 1 to 2 hours after oral administration, and bioavailability is usually unaffected by concurrent food ingestion. Levofloxacin has nearly 100% bioavailability[5,14]. FQs penetrate well into cerebrospinal fluid, where concentrations can exceed 50% of the corresponding plasma drug concentration[10].

FQs have extended antimicrobial activity against gram-negative organisms, gram-positive organisms, and atypical bacteria (Fig. 1). Early-generation FQs predominantly target gram-negative pathogens, especially the Enterobacteriaceae family. Second-generation FQs have even greater gram-negative coverage, with additional activity against *Pseudomonas aeruginosa*. New-

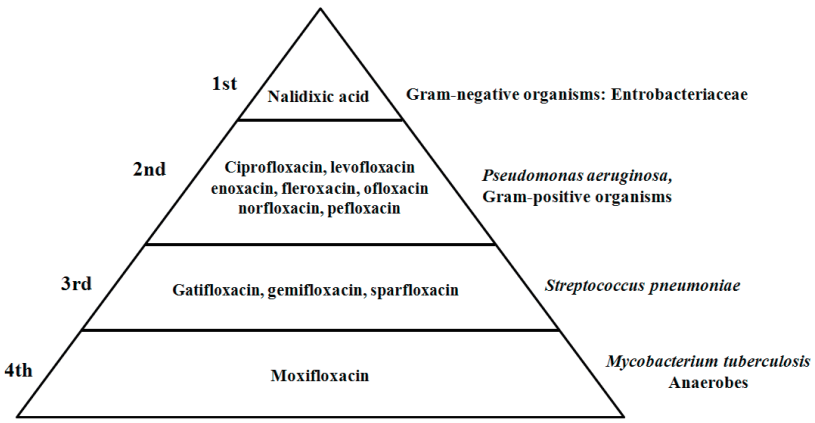

Fig. 1. Classification and antimicrobial activity of fluoroquinolones.

Table 1. Effective fluoroquinolones according to common infections

	Ciprofloxacin	Levofloxacin	Moxifloxacin
Infections	Urinary tract infections	Acute otitis media and sinusitis	Multidrug-resistant tuberculosis
	Escherichia coli	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*
	Pseudomonas aeruginosa	*Haemophilus influenzae*	
	Enterobacter species	Pneumonia	
	Citrobacter species	*Streptococcus pneumoniae*	
	Serratia species	*Mycoplasma pneumoniae*	
	Gastrointestinal infections	Multidrug-resistant tuberculosis	
	Salmonella species	*Mycobacterium tuberculosis*	
	Shigella species		
Dose			
Oral	20–40 mg/kg/day, every 12 hours (maximum 750 mg/dose)	6 months to 5 years old: 16–20 mg/kg/day, every 12 hours 5 years of age and older: 10 mg/kg/day, once daily (maximum 750 mg/dose)	Adolescents: 400 mg once daily
Intravenous	20–30 mg/kg/day, every 8 to 12 hours (maximum 400 mg/dose)	Same as oral dose	Adolescents: same as oral dose

generation FQs have enhanced activity against staphylococci, streptococci, and anaerobes. Moxifloxacin, a fourth-generation FQ, has excellent activity against many mycobacteria, including *Mycobacterium tuberculosis*[15-18] (Table 1).

Safety data regarding FQ use in children with a focus on adverse musculoskeletal events

The most common adverse effects of FQs are gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Skin rashes, allergies, and photosensitivity are also frequent. Infrequently, patients develop neutropenia, eosinophilia, and elevated liver enzymes (1–4%). All of these adverse effects are typically transient and reversible with conservative management[16,17].

Preclinical studies of quinolones in juvenile beagle dogs revealed articular cartilage damage in weight-bearing joints[19-21]. This finding restricted the general use of FQs in pediatric patients, given concern for the occurrence of similar adverse effects in growing children. Case reports of FQ-associated tendon disorders, like tendinitis and tendon rupture, have demonstrated that these injuries tend to occur in elderly patients, with the Achilles tendon being the most commonly injured[19,22]. The tendon symptoms generally develop during the first 1–2 weeks following initiation of FQ treatment, while tendon rupture typically occurs 2–3 weeks after FQ initiation[19]. In a case-control study, Achilles tendon disorders associated with FQ exposure were found to be relatively rare, with an overall risk estimated at 3.2 cases per 1,000 patient-years. Concomitant corticosteroid use appears to increase that risk substantially[22]. To date, there have been no reports of Achilles tendon rupture in children following FQ administration.

Chalumeau et al.[23] reported results from a prospective, multicenter, observational, cohort study that compared potential adverse events in 276 pediatric patients who received FQs and 249 matched controls who received an antibiotic agent other than FQ. The odds ratio (OR) and adjusted OR for potential adverse events in the FQ group were 3.7 (95% confidence interval [CI], 1.9 to 7.5) and 3.0 (95% CI, 1.5 to 5.9), respectively. The most commonly affected systems were the gastrointestinal followed by musculoskeletal (arthralgias of large joints or myalgias but no tendinopathy), skin, and central nervous systems. Adverse musculoskeletal events occurred more frequently in the FQ group than in the controls (3.8% vs. 0.4%); the crude OR for musculoskeletal potential adverse events in the FQ group was 9.3 (95% CI, 1.2 to 195). Although adverse events did occur more frequently with FQ treatment, all cases were transient, and no severe or persistent musculoskeletal injuries were observed at follow-up.

A large, prospective safety study conducted by Bayer compared (1) intravenous ceftazidime with intravenous ciprofloxacin, permitting oral step-down therapy, and (2) oral ciprofloxacin with oral cefixime or trimethoprim-sulfamethoxazole for the treatment of complicated urinary tract infections in children aged 1–17 years[18,24]. One of the primary objectives of the study was to evaluate musculoskeletal safety with ciprofloxacin therapy. At 6 weeks follow-up, the arthropathy rate was 9.3% (31/335) in the ciprofloxacin-treated group and 6.0% (21/349) in the control group (95% CI, –0.8 to 7.2), and cumulative arthropathy rate at 1 year follow-up was 13.7% and 9.5%, respectively (95% CI, –0.6 to 9.1).

In a systematic review of ciprofloxacin safety in 16,184 children from 105 studies, 258 musculoskeletal adverse events occurred in 232 pediatric patients (estimated risk, 1.6; 95% CI, 0.9 to 2.6), approximately 1 musculoskeletal adverse event for every 62.5 patients. Arthralgia was the most commonly reported adverse musculoskeletal event (50%), most frequently affecting the knee joint. Patient age at occurrence of arthropathy ranged from 7 months to 17 years (median age, 10 years). Musculoskeletal events were reversible through conservative management, which included cessation of antibiotics. Analysis of the pooled safety data from 23 controlled trials in this review showed that there was a 57% increased risk of arthropathy in the patients receiving ciprofloxacin compared to that in patients in the control arm (OR, 1.57; 95% CI, 1.26 to 1.97)[25].

Kaguelidou et al.[26] performed a systematic literature search from 1966 to July of 2009 to evaluate the efficacy, safety, and pharmacokinetics of ciprofloxacin in neonates. The study population for this review included 308 ciprofloxacin-treated patients and 692 controls from 5 cohort studies, as well as 143 ciprofloxacin-treated neonates from 27 case reports or series. Ciprofloxacin was used in neonates as a salvage therapy for sepsis caused by multidrug-resistant pathogens or for clinical exacerbation after first-line antibiotic therapy. No serious adverse events were observed. Analysis of the short-term and long-term effects of ciprofloxacin on cartilage and growth indicated no significant differences between ciprofloxacin and control groups with respect to these factors. Using multiple-regression modeling and adjusting for weight and gestational age at birth, 2 of the studies showed no significant relationship between ciprofloxacin use and the cartilage size of the right knee, as measured by ultrasound[27], and no height differences at 12 months corrected age[28].

Noel et al.[29] investigated the safety profile of levofloxacin in 2,523 children using data from 3 multicenter efficacy trials. Spontaneous reports of 1 or more musculoskeletal adverse events (arthritis, arthralgias, tendinopathy, or gait abnormality) were higher in levofloxacin-treated children than in those treated with non-FQ antibiotics at both 2-month (2.1% vs. 0.9%, P=0.04)

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and 12-month follow-ups (3.4% vs. 1.8%, *P*=0.03). However, long-term outcomes of children with musculoskeletal adverse events during the 5-year safety study were slightly higher in the control group (2.0% vs. 4.0%)[18]. Of note, current studies are investigating moxifloxacin safety in the pediatric population[30,31].

Use of systemic FQs in children

Despite the limited indications for the use of FQs in the pediatric population and concerns for adverse events, approximately 520,000 FQ prescriptions were written for patients younger than 18 years in the United States (US) in 2002. An estimated 13,800 of those prescriptions were for children 2–6 years of age, and 2,750 were written for those 2 years and younger[15]. Although there have been no systemic data on FQ use in children in Korea, 1 study, which analyzed the antibiotic prescription patterns of pediatricians and ENT (ear, nose, and throat) physicians, reported that the proportion of quinolones prescribed was 3.5% (539/15,396) during an 1-year period. These data should be interpreted with caution, as they were collected from prescription sheets in 7 community pharmacies within Ulsan City, Korea[32]. More data are clearly needed to assess FQ use in Korean children.

1. Approved indications of FQs in children

Currently, FQs that are approved by the U.S. Food and Drug Administration (FDA) for use in children include ciprofloxacin for the treatment of inhalation anthrax, complicated urinary tract infections, and pyelonephritis along with levofloxacin for inhalational anthrax[15,18]. Ciprofloxacin is the only FQ approved by the European Medicines Agency for use in the following pediatric conditions: bronchopulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*, complicated urinary tract infections, pyelonephritis, and inhalation anthrax (both for postexposure prophylaxis and curative treatment)[33]. Ciprofloxacin and levofloxacin are available as oral suspensions in many countries. An oral suspension of ciprofloxacin is available in the US, Canada, and 15 European countries[34], but systemic FQ use is not approved in Korea for any indication in children younger than 18 years. Additionally, oral suspensions are not available in Korea.

2. Organizational guidelines for FQ use in children

The World Health Organization (WHO) has provided guidelines for the management of common illnesses in hospitals with limited resources. In the WHO Pocket Book of Hospital Care for Children, ciprofloxacin is recommended as a suitable first-line agent for the treatment of dysentery (oral 10–15 mg/kg per dose given twice per day for 5 days, maximum 500 mg per dose), but its use in children is only warranted if the benefits outweigh the risk of arthropathy[35]. In the 18th WHO Expert Committee meeting for "The Selection and Use of Essential Medicines," the committee concluded that the effectiveness and safety of FQs in the treatment of life-threatening bacterial infections, such as resistant tuberculosis, dysentery, and cholera, in children have been sufficiently established[36].

In 2006, the American Academy of Pediatrics (AAP) published a policy statement summarizing the assessment of risks and benefits of FQs in pediatric patients[15]. According to the AAP, situations in which FQs may be useful include multidrug-resistant infections for which there is no safe and effective alternative, and when parenteral therapy is not feasible and no other effective oral agent is available. The AAP recommendations for FQ use in children are as follows:

- Exposure to aerosolized *Bacillus anthracis* to decrease the incidence or progression of the disease (FDA licensed)
- Urinary tract infections caused by *P. aeruginosa* or other multidrug-resistant, gram-negative bacteria (FDA licensed for complicated *Escherichia coli* urinary tract infections and pyelonephritis attributable to *E. coli* in patients 1–17 years old)
- Chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa*
- Chronic or acute osteomyelitis or osteochondritis caused by *P. aeruginosa* (but not for prophylaxis of nail puncture wounds to the foot)
- Exacerbation of pulmonary disease in patients with cystic fibrosis who are colonized with *P. aeruginosa* and can be treated in an ambulatory care setting
- Mycobacterial infections caused by isolates known to be susceptible to FQs
- Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present
- Gastrointestinal tract infections caused by multidrug-resistant *Shigella* species, *Salmonella* species, *Vibrio cholerae*, or *Campylobacter jejuni*
- Documented bacterial septicemia or meningitis attributable to organisms with in vitro resistance to approved agents or in immunocompromised infants and children in whom parenteral therapy with other appropriate antimicrobial agents has failed
- Serious infections attributable to FQ-susceptible pathogen(s) in children with a life-threatening allergy to alternative agents

As data on the musculoskeletal safety of FQs in the pediatric population accumulate, more guidelines recommend FQ use in children. In the 2011 clinical practice guidelines for community-acquired pneumonia (CAP) in infants and children by the

Pediatric Infectious Diseases Society and the Infectious Diseases Society of America (IDSA)[37], levofloxacin was recommended in certain situations as an alternative treatment option for *Streptococcus pneumoniae*, *Haemophilus influenzae* (typeable [A–F] or nontypeable), *Mycoplasma pneumoniae, Chlamydia trachomatis*, and *Chlamydia pneumoniae*. Levofloxacin is preferred in oral therapy (step-down therapy or mild infection) for CAP caused by penicillin-resistant *S. pneumoniae* in skeletally mature adolescents. Moxifloxacin is recommended as an alternative oral agent for CAP caused by *M. pneumoniae* and *Chlamydia* species in skeletally mature adolescents. In addition, levofloxacin is now recommended in children as a treatment option for acute bacterial rhinosinusitis according to the IDSA clinical practice guideline (2012) for acute bacterial rhinosinusitis in children and adults[38]: with a history of type I hypersensitivity to penicillin, as a second-line agent for children with risk for antibiotic resistance, failed initial therapy, or severe infection requiring hospitalization. Updated WHO guideline from 2011 for drug-resistant tuberculosis recommended that second-line antituberculosis regimens should include a later-generation FQ such as levofloxacin, moxifloxacin, or gatifloxacin[39].

Conclusions

Although concerns about potential musculoskeletal adverse effects in young children treated with FQs remain, many previous studies have repeatedly shown no significant increase in musculoskeletal complications in these children. In a review article, Schaad[40] commented that the triad of feared arthrotoxicity, potential explosion in bacterial resistance, and enormous requirements regarding adequate study and postmarketing control would make it unlikely that FQs will ever be recommended for treating common infections in children.

However, clinicians today are facing more situations when the use of FQs should be considered in treating pediatric patients who have not responded to standard therapy and those who are infected with multidrug-resistant pathogens, including tuberculosis. In addition, in areas with restricted medical resources, FQs may be the only option for the treatment of serious infections, especially when parenteral drug administration is not available.

In conclusion, FQs should not be used in pediatric patients for routine infections when other safe and effective antimicrobials are available. However, FQs should be considered in life-threatening and difficult-to-treat infections when alternative agents cannot be used.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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