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Review

Appropriate use of fluoroquinolones in children

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ABSTRACT

With the increasing resistance to antibiotics among common bacterial pathogens, challenges associated with the use of fluoroquinolones (FQs) in paediatrics have emerged. The majority of FQs have favourable pharmacokinetic properties, although these properties can differ in children compared with adults. Moreover, all FQs have broad antimicrobial activity both against Gram-positive and Gram-negative bacteria. However, only some FQs for which adequate studies are available have been approved for use in children in a limited number of clinical situations owing to the supposed risk of development of severe musculoskeletal disorders, as demonstrated in juvenile animals. Recent short- and long-term evaluations appear to indicate that, at least for levofloxacin, this risk, if present at all, is marginal. This marginal risk could lead to more frequent use of FQs in children, even to treat diseases for which several other drugs with documented efficacy, safety and tolerability are considered the first-line antibiotics. However, for most of the FQs, adequate long-term studies of safety are not available. This indicates that the use of FQs should be limited to selected respiratory infections (including tuberculosis), exacerbation of lung disease in cystic fibrosis, central nervous system infections, enteric infections, febrile neutropenia, as well as serious infections attributable to FQ-susceptible pathogen(s) in children with life-threatening allergies to alternative agents. When considering diseases that could benefit from the use of FQs, particular attention must be paid to the choice of drug and its dosage, considering that not all of the FQs have been evaluated in different diseases.

1. Introduction

With the increasing resistance to antibiotics among common bacterial pathogens [1,2], challenges regarding the potential use of fluoroquinolones (FQs) in paediatrics have emerged. All FQs possess broad antimicrobial activity both against Gram-positive and Gram-negative rod bacteria. However, the most established compounds, such as norfloxacin, ciprofloxacin (CIP) and ofloxacin, are particularly active against Gram-negative bacteria, including *Pseudomonas aeruginosa*, and atypical bacteria. In contrast, FQs that have been synthesised more recently, such as levofloxacin (LFX), demonstrate an increased efficacy against Gram-positive bacteria such as *Streptococcus pneumoniae* while retaining activity against many Gram-negative pathogens [3,4]. Finally, the more recent drugs in this group, such as moxifloxacin (MFX), display activity against several anaerobes and *Mycobacterium tuberculosis* while maintaining activity against aerobes similarly to that present in the previously marketed compounds [3,4].

Several FQs have been licensed for use in adults, particularly for the prevention or treatment of a number of bacterial diseases, including infections of the respiratory, intestinal and urinary tracts, skin and soft tissue, bone and joint, and eye and ear [3]. In contrast, FQs have not been widely accepted for use in children. Currently, FQs approved by the US Food and Drug Administration (FDA) for use in children include CIP for the treatment of inhalation anthrax, complicated urinary tract infections (cUTIs) and pyelonephritis as well as LFX for inhalational anthrax [5,6]. CIP is the only FQ that has been approved by the European Medicines Agency (EMA) for use in the following paediatric conditions: bronchopulmonary infections in cystic fibrosis (CF) caused by *P. aeruginosa*; cUTIs; pyelonephritis; and inhalation anthrax (both for post-exposure prophylaxis and curative treatment) [7,8].

There is evidence showing that FQs can cause significant changes in the immature cartilage of the weight-bearing joints of animals associated with defects in the epiphyseal plate, suggesting a potential negative interference with final bone development [9–11]. Gait abnormalities in these animals were reversible, but lesions were detectable histologically even several months after treatment [12,13]. In the exposed animals, the clinical manifestation of lesions presented as acute arthritis with joint effusion,

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limping or swelling that tended to disappear with time following drug withdrawal. However, despite the resolution of joint symptoms, erosion of the weight-bearing articular joint surfaces as long as 5 months after therapy can be documented [14]. Despite these findings, FQs were and are frequently used off-label in children, particularly for the treatment of severe bacterial infections [5]. Only a very small number of patients with suspected FQ-associated musculoskeletal disorders have been reported [15], leading to the broad opinion that the occurrence of the toxicity observed in juvenile experimental animals is marginal in humans. Thus, the relevance from a clinical perspective is that greater use of FQs than that officially recommended may be possible without significant risks for paediatric patients. Moreover, the pharmacokinetic characteristics of many FQs have been evaluated in the paediatric population, resulting in determination of the best dosage of each drug in children of different ages. In the present study, the available evidence regarding the use of the most largely prescribed FQs in paediatrics is discussed to provide reasonable suggestions for the rational use of these drugs in children.

2. Pharmacokinetic characteristics

Data regarding the pharmacokinetic characteristics of FQs in children are scarce, but the available information appears to indicate that these data can differ from those reported in adults and can be strictly compound-dependent. However, in most cases the available data can be considered adequate to establish effective dosages in children of any age.

2.1. Ciprofloxacin

A study conducted by Peltola et al. showed that the mean elimination half-life of CIP in children aged 1–5 years was significantly shorter than that reported in adults, which led to the suggestion that a thrice daily dosing regimen is needed in these patients to obtain the best clinical results [16]. However, as expected due to their reduced renal efficiency, infants experienced a higher systemic exposure due to reduced plasma clearance and thus, similarly to adults, they required administration only twice daily (b.i.d.). It was concluded that twice daily doses of 10–15 mg/kg/day varying by age should be adequate for maximising the beneficial effects of the treatment and obtaining the same results previously reported in adults. However, children with CF have significantly shorter half-lives of CIP, similar to previous reports with many other drugs [17,18]. This suggests the need for higher or more frequent administration schedules. In particular, it has been suggested that daily doses must be no lower than 30 mg/kg/day intravenous (i.v.) or 40 mg/kg/day oral.

2.2. Levofloxacin

Regarding LFX, data collected in healthy children following administration of a single LFX dose of 7 mg/kg demonstrated that absorption and distribution of this drug are not age-dependent and are comparable with those in adults [19]. In contrast, LFX elimination is strictly related to age. Children <5 years of age cleared LFX nearly twice as fast (i.v. dose, 0.32 ± 0.08 L/h/kg; oral dose, 0.28 ± 0.05 L/h/kg) as adults. As a result, total systemic exposure [area under the plasma drug concentration–time curve (AUC)] was approximately one-half of the levels observed in adults. Based on this premise, children ≥5 years of age require a daily dose of 10 mg/kg to provide LFX exposures similar to those associated with clinical effectiveness and safety in adults [19]. In contrast, children 6 months to 4 years of age require dosing at 10 mg/kg every 12 h (q12h) to achieve the same goal [19]. These doses were used in most of the clinical trials from which data regarding the efficacy and safety of the drug were derived. However, a recent study conducted in children with multidrug-resistant tuberculosis (MDR-TB) highlighted that, together with age, the drug formulation might play a role in conditioning the final results when this dose and even higher doses are administered [15]. In children <8 years old, LFX doses of ca. 15 mg/kg administered as whole or broken tablets [AUC to minimum inhibitory concentration ratio (AUC/MIC) of >100 and to peak drug concentration to MIC ratio (C_{max}/MIC) of 8–10] did not achieve the proposed pharmacodynamic targets needed for LFX to eradicate *M. tuberculosis*.

2.3. Moxifloxacin

Data similar to those shown for CIP and LFX were collected for MFX [20]. A total of 33 children (median age, 11.1 years) with TB who received MFX at a dose of 10 mg/kg/day as part of MDR-TB treatment were evaluated. Exposure to MFX was lower than that achieved with a standard dose of 400 mg in adults despite the slightly higher mg/kg dose administered to children. In addition, in this case the difference was attributed to a more rapid elimination of the drug in children (serum half-life for MFX of 4 h in these subjects compared with 7–10 h previously determined in adults).

3. Main clinical trials

3.1. Respiratory infections

Arguedas et al. [21] and Noel et al. [22] studied LFX in 204 children aged <5 years with difficult-to-treat acute otitis media (AOM), i.e. subjects with recurrent or persistent AOM or AOM treatment failure.

The first authors conducted an open-label, multicentre trial that involved tympanocentesis at study entry and then selectively 3–5 days after starting LFX (10 mg/kg b.i.d. for 10 days) [21]. In total, 105 isolates of *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes* were recovered in pure or mixed cultures. All of the isolates were susceptible to LFX. During the treatment, bacterial eradication from middle ear fluid occurred in 88% of the bacteriologically evaluable patients, including 90% of the children ≤2 years of age. Bacteria that were initially isolated from middle ear fluid were eradicated in 31 (84%) of 37 children infected with *S. pneumoniae* and in 54 (100%) of 54 children infected with *H. influenzae*. Overall, the clinical success rate after therapy was 94% for the total study population and 92% for the bacteriologically evaluable cases [21].

Noel et al. performed an evaluator-blinded, active-comparator, non-inferiority, multicentre study in which 1305 children (aged 6 months to <5 years) were randomised 1:1 to receive LFX (10 mg/kg b.i.d.) or amoxicillin/clavulanic acid (AMC) (amoxicillin 45 mg/kg b.i.d.) for 10 days. Children were evaluated during the drug administration from 2–5 days and 10–17 days after completing the therapy [22]. Cure rates were ca. 70% in both groups immediately after the end of therapy and ca. 2 weeks later, even in children aged ≤2 years, suggesting that LFX treatment was non-inferior to the comparator in all of the treated children.

LFX was also evaluated in an open-label, multicentre, non-inferiority trial conducted by Bradley et al. in children with community-acquired pneumonia [23]. LFX was administered for 10 days oral or i.v. at a dose of 20 mg/kg/day delivered in two doses in children aged <5 years and at 250 mg and 500 mg once daily in patients aged ≥5 years weighing 22.5–27.5 kg and >45 kg, respectively. As comparators, standard doses of AMC or ceftriaxone were administered in younger children, whereas clarithromycin or ceftriaxone with clarithromycin or erythromycin lactobionate were administered in older children [23]. A total of 539 patients

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