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Fluoroquinolones in Paediatrics

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Abstract

Fluoroquinolones have a broad spectrum of activity against Gram-positive, Gram-negative, and mycobacterial organisms as well as anaerobes, *Mycoplasma*, *Chlamydia*, *Ureaplasma*, and *Legionella* spp. They have excellent oral bioavailability, with good tissue penetration, and long elimination half-lives.

The experience with fluoroquinolones in paediatrics has been limited because of concerns about arthropathy, based on findings in animal models. However, there has not been a definitive fluoroquinolone-associated case of arthropathy described in the literature.

We believe that there are a number of specific paediatric infections in which the clinical efficacy and tolerability of the fluoroquinolones should be further investigated. These include patients with cystic fibrosis who have repeated infections with *Pseudomonas* spp., patients with pseudomonal and other Gram-negative infections such as urinary tract infections and osteomyelitis, and febrile neutropenic patients. Meningeal infections caused by multiple drug-resistant *Streptococcus pneumoniae* and Gram-negative organisms, gastroenteritis due to enteric pathogens, and mycobacterial infections are other potential conditions where fluoroquinolones should be studied in paediatric patients.

Quinolones have been an established class of antimicrobial agents for the past decade. Indeed, nalidixic acid (the parent drug of current fluoroquinolones) has been available since 1962. It was used almost exclusively for treating and preventing urinary tract infections, given its good Gram-negative coverage, excluding *Pseudomonas aeruginosa.* The new generation fluoroquinolones, including ciprofloxacin, norfloxacin, and levofloxacin, have the advantage of broader activity against Gram-positive organisms and *P. aeruginosa*.

Despite extensive clinical experience in adults, these drugs have not been widely used in paediatrics because of concerns about joint toxicity arising from animal studies which showed adverse effects on the growth plate of weight-bearing extremities in various models. There is increasing evidence, however, that this phenomenon may not apply to humans (see section 1.2).

The purpose of this communication is to review the current literature to determine whether the use of fluoroquinolones in infants and children is justified, and to identify specific indications in which they would be most beneficial.

1. Arthropathy in Children

1.1 Studies in Animals

The concern regarding arthropathy in children stems from studies in animals (including rabbits, dogs, rats, marmosets, monkeys, ferrets, and guinea-pigs), which showed the development of large joint arthropathy after exposure to all quinolones studied, including ciprofloxacin and nalidixic acid.[1,2] The extent of the arthropathy was species dependent as well as dose dependent.

Histopathologically, blisters, fissures and erosions were seen within days to weeks, and progressed to cavitations. Chondrocyte necrosis and cartilage dissolution have been observed by electron microscopy.[3] The effect was generally more pronounced in younger animals with immature cartilage; however, pefloxacin caused arthropathy in skeletally mature and immature dogs.[4] Studies in beagle puppies showed that arthropathy was diminished with decreased weight bearing, suggesting that stress on the joints could be an important cofactor.[5] Interestingly, Ingham et al.[6] showed

that, in dogs, clinical arthropathy syndrome was reversed after treatment was stopped.

The pathogenesis of arthropathy is not well understood. It is hypothesised that it could be related to the following: (i) the anti-DNA gyrase action of quinolones causing inhibition of the DNA synthesis of chondrocytes; (ii) quinolone-induced oxidative injury to chondrocytes; (iii) compromised mitochondrial integrity; or (iv), most recently, magnesium ion chelation by quinolones, leading to altered function of chondrocyte surface integrin receptors, which play a role in maintaining the integrity of cartilage matrix.[2]

1.2 Studies in Children

As arthropathy was seen with all quinolones tested in young animals, this promoted concerns of cartilage toxicity leading to growth suppression in children and young adults with non-fused epiphyses. For this reason, fluoroquinolones were never approved for use in paediatrics. Ironically, nalidixic acid, which of all quinolones showed the strongest arthropathic effect in animals, was approved in 1962 for use in paediatrics and used routinely to treat urinary tract infections.

There are limited data on use of quinolones in paediatrics. Schaad and Wedgwood-Krucko[7], who reviewed the experience with nalidixic acid in 11 children (aged 3 months to 9 years) treated with the drug for several months, found no evidence of arthropathy in any patient. This raises the possibility that humans may have a higher threshold for arthropathy compared with other species

Ciprofloxacin has been used in patients with cystic fibrosis because of its antipseudomonal activity as an oral agent. Schaad et al.[8] found no adverse articular effects [determined by roentgenography and magnetic resonance imaging (MRI)] in 18 patients treated with ciprofloxacin for up to 3 months and followed for close to 2 years. Furthermore, Warren[1] found no evidence of significant arthropathy in patients with cystic fibrosis treated with ciprofloxacin. After a review of 31 reports describing use of ciprofloxacin, nalidixic acid, pefloxacin, norfloxacin, or ofloxacin in 7045 patients (aged between 5 days and 24 years), Burkhardt et al.[2] concluded that there were no definitive cases of quinolone-associated arthropathy.

In addition to patients with cystic fibrosis, studies on the use of quinolones (including norfloxacin, ciprofloxacin and trovafloxacin) in children with other conditions such as shigellosis, salmonellosis and meningococcal meningitis, reported no cases of arthropathy.[9-13]

On the basis of this limited experience and the potential usefulness of the fluoroquinolones in paediatric infections, the Food and Drug Administration has signalled its willingness to consider protocols to study these agents in selected conditions in infants and children.

2. Summary of Antibacterial Spectrum of Fluoroquinolones

Ciprofloxacin has a wide spectrum of antimicrobial activity encompassing Gram-negative bacilli (including *P. aeruginosa*), and staphylococci. In addition, it also has activity against mycobacteria, but is less active against pneumococci, *Mycoplasma* and *Chlamydia* spp., and anaerobes.[14]

Because of greater activity compared with ciprofloxacin against Gram-positive cocci (including multidrug-resistant pneumococci) and anaerobes, the new generation fluoroquinolones such as trovafloxacin, gatifloxacin, clinafloxacin, and moxifloxacin look promising for use in paediatrics.[15] Ciprofloxacin is the most active among the quinolones tested against *P. aeruginosa*; however, clinafloxacin and trovafloxacin have activity that is nearly comparable to ciprofloxacin.[15] Trovafloxacin has *in vitro* activity comparable to metronidazole against *Bacteroides fragilis* and *Clostridium perfringens*, and better than metronidazole against *Peptostreptococcus magnus*.[15,16]

3. Clinical Efficacy – Potential Indications

Because of the unique epidemiological pressures exerted in daycare management of infants and children, and the concern for emergence of resistance, fluoroquinolones should not be used routinely for common infections (e.g. acute otitis media). The following section reviews available data on the use of this class of drugs in patients with difficult-to-treat infections.

3.1 Cystic Fibrosis

The experience with fluoroquinolones, especially ciprofloxacin, is greatest in this group of paediatric patients.[17-20] This is because these patients are chronically colonised with *P. aeruginosa*, and develop frequent acute exacerbations of lower respiratory tract disease. *Staphylococcus aureus* and occasionally non-tuberculous mycobacteria can be copathogens in these patients.

Richard et al.[17] reported 108 patients with cystic fibrosis who were randomised to receive either oral ciprofloxacin 750mg twice daily or intravenous ceftazidime plus tobramycin therapy for 14 days. 93% of patients showed clinical improvement in the ciprofloxacin group compared with 96% in conventionally

treated patients. Arthropathy was not observed in any patient (determined by ultrasonography and MRI). Transient suppression of *P. aeruginosa* was found in 63% of the ceftazidime-tobramycin group but in only 24% of those given ciprofloxacin. Sequential intravenous-oral ciprofloxacin was as effective and safe as intravenous ceftazidime and tobramycin for a minimum of 10 days in 84 cystic fibrosis patients (aged 5 to 17 years) in a double-blind study.[18] In addition, maintenance therapy with ciprofloxacin for 3 months was as effective as a 14-day regimen of intravenous ceftazidime and amikacin, supplemented by inhaled amikacin, in reducing acute exacerbations of respiratory disease in 44 patients with cystic fibrosis.[19]

More than 800 children and adolescents with cystic fibrosis have received oral ciprofloxacin for periods of 10 days to 6 months without documented adverse effects or intolerance.[21] In addition to ciprofloxacin, pefloxacin and ofloxacin and new generation quinolones such as clinafloxacin and trovafloxacin may also be useful in these patients because of their excellent antipseudomonal activity[15] and oral bioavailability.[22,23] Photosensitivity may limit the usefulness of clinafloxacin in paediatric patients.

3.2 Meningitis

The increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* isolates is a concern worldwide. Fortunately, drug concentrations required for antibacterial activity can still be achieved in many tissues, including the lungs, with larger dosages of penicillin or ampicillin given intravenously. However, central nervous system (CNS) infections caused by resistant *S. pneumoniae* are a challenge because CNS concentrations of β-lactam antibiotics may not be maintained above the minimum inhibitory concentration (MIC) long enough for bacterial eradication. Although ciprofloxacin does not have good activity against *S. pneumoniae*, the new generation of fluoroquinolones, especially trovafloxacin, gatifloxacin, and moxifloxacin, have excellent activity against even the highly penicillin- and cephalosporin-resistant pneumococci, thereby allowing effective bactericidal activity in the CNS.[15,24-27] Data from the rabbit meningitis model showed excellent bacteriological effectiveness of trovafloxacin, gatifloxacin, and moxifloxacin in meningitis caused by resistant pneumococci.[24-27]

In a study of meningococcal meningitis in 187 African children, a cure rate of around 90% was achieved with 5 days of trovafloxacin therapy (given orally in 70% of cases), and was similar to that of ceftriaxone therapy.[13] Trovafloxacin is currently being evaluated in a large multicentre trial as therapy for bacterial meningitis in children.

Besides *S. pneumoniae*, another potential indication for fluoroquinolones is multidrug-resistant Gram-negative meningitis in neonates and immunocompromised children. Trovafloxacin has excellent oral bioavailability and bactericidal activity against causative pathogens of bacterial meningitis. Thus, it may be particularly useful in areas where bacterial resistance is a problem and prolonged parenteral therapy is not feasible. Gatifloxacin also looks promising in this indication, having shown activity in an animal model of bacterial meningitis caused by Gram-negative organisms.[26]

Among the neonates, besides Gram-negative organisms, pathogens such as *Listeria monocytogenes*, Group B streptococci, and *Mycoplasma hominis* are also susceptible to trovafloxacin, gatifloxacin, moxifloxacin, and clinafloxacin.[14,15,28]

3.3 Febrile Neutropenia

Neutropenia is a predictable consequence of cancer chemotherapy putting patients at risk of developing invasive infections, most frequently bacterial in origin. Treatment usually consists of empirical broad-spectrum antibiotic therapy, primarily to cover Gram-negative bacilli, including *P. aeruginosa*. Gram-positive cocci such as *S. epidermidis*, *S. aureus* and α-haemolytic streptococci, account for the second major group of pathogens affecting immunocompromised patients. These patients are also at risk from infection with multidrug-resistant organisms because of repeated courses of broad-spectrum antibiotics and use of antimicrobial prophylaxis.

Freifeld and Pizzo[29] reviewed 8 reports on the use of ciprofloxacin, norfloxacin and ofloxacin as empirical therapy of febrile neutropenic episodes, and concluded that fluoroquinolones were most suitable for empirical therapy in low risk febrile neutropenic patients. Because these agents do not have reliable Gram-positive coverage, they are unsuitable for empirical therapy in high risk febrile neutropenic children.

The improved Gram-positive, and excellent Gram-negative activity of agents like trovafloxacin, gatifloxacin, and moxifloxacin should make these agents excellent candidates for use in high risk children with febrile neutropenia.

3.4 Resistant Pneumococcal Infections

Increasing resistance of pneumococcal isolates to the penicillins, macrolides, and cephalosporins is a universal concern, especially when the empirical use

of vancomycin is limited because of concerns about vancomycin-resistant enterococci (VRE) and intermediately resistant *S. aureus* (VISA) strains. Because new fluoroquinolones such as trovafloxacin, gatifloxacin, and moxifloxacin are highly active against multidrug-resistant strains of *S. pneumoniae*,[14,15,24-27] assessment of these agents is indicated in selected paediatric patients who fail initial treatment for acute otitis media and sinusitis.

3.5 Bone and Joint infections

Fluoroquinolones achieve high concentrations in bones and joints. In addition, ciprofloxacin, trovafloxacin, gatifloxacin, and moxifloxacin exhibit good activity against methicillin- susceptible *S. aureus*, and *S. pyogenes*, the 2 leading organisms in acute osteomyelitis and suppurative arthritis in immunocompetent children. However, the use of fluoroquinolones in this patient group has been limited because of concerns of arthropathy and also because of other treatment options, namely antistaphylococcal penicillins and first generation cephalosporins.

With regard to infections caused by other organisms such as penicillin-resistant *S. pneumoniae*, methicillin-resistant *S. aureus*, *Salmonella* spp.,[30,31] and, especially, *P. aeruginosa*,[32] the treatment options for oral agents are limited. In cases of pseudomonal osteochondritis, oral ciprofloxacin for up to 14 days is an adequate alternative to parenteral therapy, after appropriate drainage and curettage of the bone and cartilage.[32] Ciprofloxacin has excellent activity against *P. aeruginosa* and *Salmonella* spp., but lacks reliable activity against pneumococcus. By contrast, trovafloxacin, gatifloxacin, clinafloxacin, and moxifloxacin exhibit excellent activity against penicillin-resistant pneumococci and good Gram-negative coverage.[15] *Salmonella* or *Yersinia enterocolitica* osteomyelitis has been successfully treated with ciprofloxacin.[30,31,33]

3.6 Urinary Tract Infections (UTIs)

The new fluoroquinolones have excellent activity against Gram-negative bacilli, including *P. aeruginosa*. Since most of the UTIs are caused by Gram-negative bacilli, which may be multidrug-resistant in complicated cases, the fluoroquinolones are a logical choice for treatment, especially when an oral agent is preferred. An exception is trovafloxacin, which is primarily excreted through bile. Only about 10% is excreted in the urine,[34] making it less suitable for UTI therapy. By contrast, ciprofloxacin, norfloxacin, ofloxacin,[35] gatifloxacin and clinafloxacin are primarily excreted in the urine,[23,36] making them excellent agents to treat UTIs. In addition to their renal clearance, ciprofloxacin and norfloxacin also have a hepatic route of clearance.

Clinical experience in paediatric patients with UTIs is limited.[37] Richard et al.[38] conducted a randomised trial in 186 adult patients with acute pyelonephritis, using levofloxacin 250mg once daily, ciprofloxacin 500mg twice daily, and lomefloxacin 400mg once daily. *Escherichia coli* was the most frequent pathogen. All 3 drugs showed ≥94% eradication of pathogens at 5 to 9 days after completion of therapy. Two retrospective studies also reported successful treatment of UTIs with norfloxacin.[21]

3.7 Gastrointestinal Infections

3.7.1 Gastroenteritis

Enteric pathogens are the leading cause of bacterial diarrhoea worldwide. The choice of antibiotics is becoming limited as a result of high multidrug resistance among *Shigella*, *Salmonella*, and *Campylobacter* spp.[39-41] Fluoroquinolones offer an advantage over other classes of antibiotics because (i) most strains of *Shigella*, *Salmonella*, and *Vibrio cholerae* are susceptible to them; (ii) absorption and faecal concentrations are not affected by diarrhoea; (iii) they achieve high and sustained concentrations in the gut, allowing a short course of therapy; and (iv) high biliary concentrations may help prevent the post-treatment *Salmonella* carrier state.[21]

There is relatively broad experience with the use of fluoroquinolones in diarrhoeal illnesses in children. In a randomised, double-blind trial in 201 children, ciprofloxacin was found to be as effective and safe as ceftriaxone.[11] In addition, norfloxacin-treated children had a significantly shorter duration of diarrhoea in comparison with nalidixic acid in 59 children with shigellosis.[9] In 21 children with multidrug-resistant typhoid fever with diarrhoea, ciprofloxacin was as successful as furazolidone.[40]

Ciprofloxacin was found to be a useful agent in a review of its use in the treatment of shigellosis, invasive salmonellosis, cholera and *E. coli* gastroenteritis in developing countries.[10] Ciprofloxacin, 500mg twice for one day, was as effective as a 3-day doxycycline regimen in adults with *V. cholerae* diarrhoea.[42]

There are reports from Southeast Asia and Spain of quinolone resistance among *Salmonella* and *Shigella* strains,[43-45] which could pose a problem for future treatment of these infections. In addition, *Campyobacter* spp. have been reported to have a high rate of quinolone resistance in Spain.[41] Clinafloxacin may be active against some of these strains.[46]

3.7.2 Intra-Abdominal Infections

In addition to their activity against Gram-negative pathogens and enterococci, the fluoroquinolones trovafloxacin and clinafloxacin have shown high activity against anaerobes, which makes them promising agents for the treatment of intra-abdominal infections. Trovafloxacin is approved for this indication in adults, and clinafloxacin was shown to be as efficacious as imipenem/cilastatin in this indication.[47]

3.8 Mycobacterial Infections

The new methoxyquinolone moxifloxacin has shown bactericidal activity against *Mycobacterium tuberculosis* comparable to that of isoniazid *in vitro* and in mice.[48] Atypical mycobacterial infections in children have been satisfactorily treated with ciprofloxacin as part of combination therapy,[49] and gatifloxacin has been shown *in vitro* to be active against *M. leprae*.[50]

4. Conclusions

Given the broad spectrum of activity of the fluoroquinolones and apparent lack of arthropathy in paediatric patients, these agents should be studied in selected paediatric patients, who have difficult-to-treat infections. Studies to date have shown promising results with this class of drugs in patients with cystic fibrosis, meningitis (caused by pneumococci or Gram-negative pathogens), febrile neutropenia, resistant pneumococcal infections, bone and joint infections, urinary tract infections, gastrointestinal infections (gastroenteritis and intra-abdominal infections) and mycobacterial infections. Thus, further investigation of their use in the paediatric setting is warranted. Newer agents including trovafloxacin, clinafloxacin and moxifloxacin have shown promising results.

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