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Ciprofloxacin Use in Children: A Review of Recent Findings

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Formulary Update

Since their introduction in the United States over a decade ago, the quinolones have become a mainstay in the treatment of serious bacterial infections in adults. Their use in children, however, has been restricted because of concern for potential cartilage damage. Early studies with this therapeutic class demonstrated serious cartilage erosion and joint malformations in young animals. As a result, these agents were labelled as contraindicated in children.[1,2] Despite the risk of toxicity, the need for a broad spectrum antibacterial made the use of ciprofloxacin appealing for some patient populations. To date, infants and children with multi-drug resistant infections, children with cystic fibrosis (CF), and immunocompromised children have all been successfully treated with ciprofloxacin.[1-3]

Mechanism and Spectrum of Activity

The fluoroquinolones are known for their extremely broad spectrum of antibacterial activity. They are bactericidal agents that act by interfering with the enzyme DNA gyrase to inhibit bacterial DNA synthesis.[4]

Ciprofloxacin is effective against most Gram negative organisms, including *Pseudomonas aeruginosa*, as well as Acinetobacter, Campylobacter, Haemophilus, Salmonella, and Shigella species. Some notable **exceptions** to this coverage include Flavobacterium sp., *Plesiomonas shigelloides*, *Pseudomonas fluorescens*, and *Stenotrophomonas maltophilia*. Gram positive coverage includes most species of Staphylococcus and Streptococcus, including many beta-lactam resistant strains. Ciprofloxacin is generally not active against anaerobes.

Use in Infants and Children

The majority of papers published in the pediatric population focus on the use of ciprofloxacin in children with CF. Among the most recent of these is a study published in a supplement to *The Pediatrics Infectious Disease Journal* in 1997. This was a prospective, randomized, double blind trial conducted to compare the efficacy and safety of ciprofloxacin to the combination of ceftazidime and tobramycin in children with CF during an acute pulmonary exacerbation associated with *Pseudomonas aeruginosa* infection.[5]

One hundred and thirty patients were enrolled and randomized to receive either ciprofloxacin at a dose of 10 mg/kg IV every 8 hours for 7 days followed by 20 mg/kg PO every 12 hours for 3 days or ceftazidime 50 mg/kg every 8 hours plus tobramycin 3 mg/kg every 8 hours for 10 days. Eighty-four children (age range 5 to 17 years) completed the study. All demonstrated clinical improvement, based on pulmonary function tests and clinical scores. Three ciprofloxacin-treated patients and 2 combination patients relapsed within the 4 week follow-up period. Adverse effects were similar in both groups; none required discontinuation of treatment.

In a follow-up study, the same authors evaluated oral ciprofloxacin alone (15 mg/kg given twice daily) versus ceftazidime plus tobramycin for 2 weeks in children with CF. One hundred and eight patients, ages of 5 to 17 years, were enrolled in this randomized multicenter trial.[6] Clinical improvement was comparable, 93% in the ciprofloxacin patients and 96% in those receiving combination IV therapy. Transient reduction in colonization with *Pseudomonas aeruginosa*, however, was seen in up to 63% of patients on combination therapy, but only 24% of the ciprofloxacin group. No serious adverse effects were noted in either treatment group.

In addition to the treatment of exacerbations, ciprofloxacin has also been studied as maintenance antipseudomonal therapy in children and young adults with CF. Recently, an open-label trial was conducted which included two arms: oral ciprofloxacin 30 mg/kg/day alone or combined with inhaled amikacin 500 mg/day.[7] The study was conducted in 44 outpatients over a 3 month period. The majority of the patients in each arm showed clinical improvement. There were 4 treatment failures (1 ciprofloxacin alone, 3 combination).

Other populations who might benefit from ciprofloxacin include children with diseases resulting in immunocompromise and those with neutropenia from cancer chemotherapy. The use of fluoroquinolones as prophylactic agents was reviewed by a group from St. Jude Children's Research Hospital in 1995.[8] The authors concluded that prophylaxis was effective in preventing Gram negative bacterial infections in immunocompromised children, but that patients were at greater risk for Gram positive superinfections. In a companion review, Freifeld and Pizzo from the National Cancer Institutes of Health evaluated fluoroquinolone use as empiric treatment for these patients.[9] The authors provide similar conclusions: the class is effective, but their use must be weighed with potential risk for toxicity.

Pharmacokinetics

Ciprofloxacin is well absorbed after oral administration and is widely distributed throughout the body. Like other fluoroquinolones, it is both metabolized and excreted unchanged in the urine.[4] There have been a number of ciprofloxacin pharmacokinetic studies conducted in adults, including patients with CF. These studies have provided consistent results, with an average volume of distribution of 2 to 3 L/kg and an elimination half-life of 4 to 5 hours. Patients with CF have not been shown to differ in their drug elimination compared to matched controls.[10]

In contrast to the amount of research in adults, there are only a few studies of ciprofloxacin pharmacokinetics in children. In 1992, Peltola and colleagues studied 16 infants and children treated with ciprofloxacin.[11] None of the patients had CF. The authors reported an average elimination half-life of 1.3 hours in patients less than 6 years of age. None of those children had CF. In their older patients (6-16 years), the authors reported an average half-life of 2.6 hours after IV dosing and 3.8 hours after oral dosing.

In 1997, Rubio and coworkers studied the disposition of ciprofloxacin in 18 children, ages 5 to 17 years, with CF.[12] The patients received 10 mg/kg ciprofloxacin IV every 8 hours for at least three days, then switched to 20 mg/kg ciprofloxacin PO every 12 hours. Average half-life values for the group were 2.6 ± 0.6 hours with IV dosing and 3.4 ± 0.7 hours with PO dosing. Subgroup analysis revealed no significant difference in elimination between younger and older children.

Earlier this year, a study was conducted using an investigational ciprofloxacin oral suspension in 16 children ages 0.3 to 7.1 years (none with CF).[13] The dose was 10 mg/kg given every 8 hours. Half-life values did not significantly differ among the subgroups, with values ranging from 4.2 ± 1.1 hours in patients 1 year of age to 5.1 ± 1.1 hours in children 2 to 5 years. The results of these studies suggest that ciprofloxacin pharmacokinetic parameters in children are similar to values established in adults.

Adverse Effects

The greatest concern with ciprofloxacin use in children is potential bone and joint damage. In animal models, the fluoroquinolones have been associated with a slowly progressive arthropathy characterized by fluid-filled blisters, fissures, and erosions within the joints.[2] The mechanism for this adverse effect is still unclear, but may involve both alterations in collagen deposition and changes in chondrocyte function.[14] While the risk for joint damage has caused clinicians to use caution when prescribing these agents in children, close monitoring of pediatric patients treated with ciprofloxacin has thus far failed to reveal any significant cartilage toxicity.

In 1991, the results of a world-wide surveillance study on ciprofloxacin use in children were published in the journal *Infection*.[15] Over 600 children had been treated by that time, most for pulmonary exacerbations of CF. Eight teenage girls with CF were reported to have mild arthralgias during treatment, resolving after the end of treatment. This incidence is not significantly different than the reports of joint pain in teens with CF receiving other therapies. Recently, a follow-up report of this project, now including 1,795 children has documented an overall incidence of arthralgia of 1.5%, with most being of mild to moderate severity.[16]

Magnetic resonance imaging (MRI) has been used in several studies to evaluate joint changes in children receiving ciprofloxacin. Schaad and colleagues evaluated 18 children with CF who received a 3-month course of ciprofloxacin and found no significant changes during treatment or at follow-up 4 to 6 months later.[17] In addition to the MRI findings, skeletal function tests, height velocity, laboratory testing, and physical exams also revealed no abnormal development. These researchers also examined 2 CF patients post mortem who had received several courses of ciprofloxacin.[18] Neither case suggested joint damage.

Further support for the use of ciprofloxacin comes from studies from the Slovak Republic[19] and Viet Nam[20] in 1996. In the Slovak study, 29 children with CF, ages 4 to 18 years, were given either ofloxacin or ciprofloxacin 10 mg/kg every 12 hours for 4 to 28 days. A comparison group of children without CF who had never received quinolones served as controls. Of the 14 treated patients available for evaluation, 6 developed transient arthralgias during therapy, compared to 4 of 15 control patients. Physical skeletal function exams, laboratory studies, and MRI findings revealed no differences between the treatment and control groups.[19]

A longitudinal study of height velocity from Viet Nam also failed to show any significant damage associated with quinolone use.[20] In this study, 326 children were followed for up to 2 years after receiving either ciprofloxacin or ofloxacin for suspected typhoid fever. As with the Slovak study, these children were found to be growing at a rate similar to controls.

In adults, the most frequently occurring adverse effects associated with ciprofloxacin use include nausea, abdominal pain, diarrhea, and vomiting (in 2 to 6% of patients). Other common adverse effects include headache or dizziness

(1.2%) and rash or photosensitivity (1.1%). Laboratory test changes include transient elevations in hepatic function tests (0.3-1.9%) or serum creatinine (1.1%). Studies conducted in children and case reports have revealed similar findings.[21]

Renal disease, including interstitial nephritis and renal calculi, has been reported in adults taking ciprofloxacin, but is estimated to occur in less than 1%. Hypersensitivity reactions to ciprofloxacin have also been reported, including anaphylaxis. [4] In addition, there has been one publication of ciprofloxacin causing a greenish discoloration of the teeth of 2 children who received the drug while they were infants.[22]

Drug Interactions

Ciprofloxacin, like the other quinolones, interacts with many other medications and nutrients (Tables 1 and 2). A large percentage of these interactions are the result of interference with cytochrome P450 1A2 function.[4]

Table 1. Effect of other drugs on ciprofloxacin

Antacids	↓absorption
Antineoplastics	↓ serum concentration
Azlocillin	↓ clearance[a]
Cimetidine	↓ clearance[a]
Probenecid	↓ clearance[a]

[a] increases ciprofloxacin serum concentrations

Table 2. Effect of ciprofloxacin on other drugs

Caffeine	↓ clearance[b]
Cyclosporine	nephrotoxicity risk
Phenytoin	↓ serum concentration
Theophylline	↓ clearance[b]
Warfarin	effect

[b] increases serum concentration of affected drug

Ciprofloxacin should not be given simultaneously with enteral feedings. Patients may take ciprofloxacin with food, but should be instructed to avoid taking dairy

products such as milk and yogurt, iron, or zinc supplements at the same time as a ciprofloxacin dose.

Dosing Recommendations

Ciprofloxacin (Cipro® ; Bayer) is currently available as an injection in 200mg/20 ml and 400 mg/40 ml vials, as tablets in 100, 250, 500, and 750 mg strengths, and as a oral liquid suspension 250 mg/5ml and 500 mg/5ml. Based on the studies reviewed, the usual dosage regimen for pediatric patients is 10 mg/kg given every 8 hours or 15 mg/kg given every 12 hours.

Summary

Ciprofloxacin offers a potential alternative for antimicrobial therapy in selected pediatric populations, such as children with CF. It offers the advantages of a broad spectrum of antibacterial activity, good tissue penetration, and the ease of oral administration. While recent publications have documented the safe use of this agent in children, more longitudinal studies are needed. At this time, ciprofloxacin should still be reserved for those patients in whom the risk of cartilage toxicity is clearly outweighed by its benefits.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/4/98:

1. Infliximab (Remicade®) was added to the formulary for the treatment of Crohn's disease refractory to standard measures.
2. Ofloxacin otic (Floxin®) also was added to the formulary.
3. Rotavirus vaccine (RotaShield®) was approved for the prevention of rotaviral gastroenteritis. The product is a live, orally administered vaccine given in a 2.5 ml dose at 2, 4, and 6 months.

If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.

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