PEDIATRIC PHARMACOTHERAPY

University of Virginia Children's Hospital

Volume 24 Number 8 August 2018

A Reappraisal of Ciprofloxacin Use in Infants and Children

Marcia L. Buck, PharmD, FCCP, FPPAG, BCPPS

The approval of ciprofloxacin by the Food and Drug Administration (FDA) on October 22, 1987 marked the introduction of the fluoroquinolones into the United States.[1] These drugs offer a broad antibacterial spectrum, as well as extensive penetration into deep compartments, and highly bioavailable oral formulations. By 2002, fluoroquinolones were the most commonly prescribed antibiotics in adults.[2] More than 7,500,000 prescriptions were written for ciprofloxacin in 2015, making it the 9th most frequently prescribed medication of all types in the United States. Thirty years after their introduction fluoroquinolones remain a popular option for treatment of a variety of infections, in spite of concerns over the risk for serious adverse effects with their use and the growing development of fluoroquinolone resistance. With the release of the latest FDA drug safety communication on the risks of fluoroquinolones last month, the time has come for a reassessment of their use.[3]

Ciprofloxacin Prescribing in Children

As a result of the risk for articular damage first identified with nalidixic acid, the precursor to the fluoroquinolones, the FDA has required manufacturers to include in their product labeling that these drugs are not a first choice for treatment of pediatric infections. Approved uses for ciprofloxacin in children are limited to the treatment of complicated urinary tract infections (UTIs) and pyelonephritis caused by *E. coli* not sensitive to other agents, prophylaxis or treatment of plague due to *Yersinia pestis*, and management of patients following inhalational anthrax exposure.[4]

Off-label prescribing of ciprofloxacin in children has been well documented. A recent study from Etminan and colleagues in *The Pediatric Infectious Disease Journal* evaluated oral fluoroquinolone prescribing in children in the United States between 2006 and 2015 using the PharMetrics Plus™ health claims database.[5] A total of 372,357 fluoroquinolone prescriptions were written for 2,754,431 children, with the frequency increasing each year until a peak in 2013. Ciprofloxacin was the most frequently used fluoroquinolone, accounting for 90% of the prescriptions. Nearly half of the prescriptions (48%) were written for children under 10 years of age and 22% were determined by the authors to have been inappropriate, based on guidelines for fluoroquinolone use published by the American Academy of Pediatrics in 2016.[6]

Another study of pediatric fluoroquinolone use was published by Meesters and colleagues in the February 2018 issue of *BMC Infectious Diseases*.[7] The authors analyzed the indications for systemic fluoroquinolone prescribing in children treated at two Belgian children's hospitals between 2010 and 2013. Of the 262 prescriptions evaluated, ciprofloxacin was used in all but nine. While the mean age of the patients being treated was 5.2 years (interquartile range 1.8-12.4 years), the majority of prescriptions were written for the 12 to 18-year-old group. Intravenous ciprofloxacin was used in 51% of the patients. Only 17% were for approved indications: 13 (5%) for refractory respiratory infections in children with cystic fibrosis and 31 (12%) for complicated UTIs or pyelonephritis. Most of the patients were given a fluoroquinolone as empiric treatment for central nervous system infections (representing 25% of prescriptions), respiratory tract infections or pneumonia (18%), or as prophylaxis in cancer patients with febrile neutropenia (18%). Thirty-five percent of the patients had positive bacterial cultures, with *Pseudomonas aeruginosa* being the most common organism identified.

Faghihi and colleagues found similar results in their 10-month observational study of children at the Children's Medical Center in Tehran.[8] From 14,511 hospital admissions, the authors identified 32 children who received oral or intravenous ciprofloxacin for at least 48 hours. The mean age of the patients was 8.9 $\pm$ 3.9 years (range 2-18 years). Ciprofloxacin use was more common in younger children; 25 of the patients (78%) were

less than 12 years of age. Twenty-five of the children (78%) were treated for an off-label indication. Of those, only 5 (15%) were considered justified by the authors, according to FDA and American Academy of Pediatrics guidelines or by evidence of infection with an organism resistant to standard therapy.

While these studies suggest that much of ciprofloxacin prescribing in children might be avoided, there are cases in which it remains an appropriate choice. Ciprofloxacin has been shown to be effective in the treatment of complicated pulmonary exacerbations in children with cystic fibrosis, management of refractory infections in immunosuppressed children receiving chemotherapy, and in the treatment of multidrug resistant sepsis.[9-11]

The first published account of using ciprofloxacin to treat multidrug-resistant neonatal sepsis was published in 1989.[10] Since that time, a number of case reports and case series describing its use in neonatal sepsis have appeared in print. In a 2011 systematic review, Kaguelidou and colleagues evaluated 32 papers, including 5 cohort studies and 27 single case reports or case series, confirming the earlier studies.[11] Ciprofloxacin was prescribed for sepsis caused by multidrug-resistant organisms or in the setting of a worsening clinical condition during first-line therapy. The rates of clinical response were estimated to be 64% and 91% in the two cohort studies and 83% in the cases and case series. The authors found no reports of serious adverse effects in these papers, although they acknowledge that the depth of evaluation and length of follow-up precluded making an assessment of the drug safety.

Fluoroquinolone Resistance in Children

Widespread use of fluoroquinolones has led to the development of resistance worldwide.[12-15] The first gene variant associated with increased fluoroquinolone minimum inhibitory concentrations (MICs) was identified in the 1980s. Resistance is primarily the result of mutations in the quinolone resistance determining region of DNA gyrase (*gyrA, gyrB*) and the topoisomerase IV (*parC, parE*) encoding genes which alter the conformation of amino acids within DNA gyrase and topoisomerase IV in the bacteria. Plasmid-mediated quinolone resistance genes were identified in the late 1990s. Expression of these mutations results in a reduction in fluoroquinolone uptake in bacterial cells, increased drug efflux from the cells, or drug inactivation. The March 2018 issue of *PLoS Pathogens* provides an in-depth review of fluoroquinolone resistance in Conley and colleagues' thought-provoking and entertaining article, "Wicked: the untold story of ciprofloxacin," available on-line at https://doi.org/10.1371/journal.ppat.1006805.[12]

In 2014, Rose and colleagues evaluated the prevalence of fluoroquinolone resistance in a cohort of 1,433 children treated for Gram negative bacterial infections between 2001 and 2009 at the Alfred I. duPont Hospital for Children.[13] The median age of the patients was 4 years (interquartile range 1-11 years). Use of fluoroquinolones increased from 22 doses/1000 patient-days/year in 2001 to 40 doses/1000 patient-days/year in 2008 ($p = 0.005$), with a similar rise in the length of therapy, from 14 to 23 days of treatment/1000 patient-days/year ($p = 0.004$). A total of 2,112 Gram negative infections were identified. The most commonly encountered organisms were *E. coli* (34.5%), *Pseudomonas aeruginosa* (26.5%), *Klebsiella pneumoniae* (13.7%), and *Enterobacter cloacae* (10.6%). Susceptibility to ciprofloxacin decreased from 173 of 180 cultures (96.1%) in 2001 to 341 of 365 (93.4%) in 2009 ($p = 0.003$). A similar decline was seen with levofloxacin, with susceptibility in 174 of 180 cultures (96.6%) in 2001 and 350 of 365 (95.9%) in 2009 ($p = 0.016$). Resistant isolates were most often obtained from bronchial lavage (10.4%), tracheal aspirates (6.4%), and urine cultures (5.6%). The authors found a strong correlation between the number of fluoroquinolone doses administered and the prevalence of resistance for both ciprofloxacin and levofloxacin ($r = 0.879$ and $r = 0.874$, respectively, $p < 0.001$) as well as for days of therapy and resistance ($r = 0.938$ and $r = 0.945$, $p < 0.001$).

Two papers released earlier this year highlight the growing risk for fluoroquinolone resistance in the community. In the April 2018 issue of the *Journal of Medical Microbiology*, Saksena and colleagues assessed the gut flora of antibiotic naïve neonates in New Delhi to study the presence of communal fluoroquinolone resistance.[14] Stool samples from 100 breastfed infants were collected on day of life 1, 2, and 60. A total of 343 Enterobacteriaceae were isolated. The presence of ciprofloxacin-resistant organisms increased from 15% of neonates on day of life 1 to 38% on day 60 ($p < 0.001$). Last month, Karp and colleagues found an increase in plasmid-mediated quinolone resistance in non-typhoidal Salmonella isolates submitted to the Centers for Disease Control and Prevention between 2008 and 2014. Their paper adds even greater support to the concerns being expressed over the growing loss of fluoroquinolone efficacy.[15]

FDA Drug Safety Communications

The first drug safety communication on fluoroquinolone adverse effects was issued a decade ago.[1] In July 2008, the FDA announced the addition of a black box warning to all fluoroquinolones alerting prescribers to the increased risk for tendinitis and tendon rupture during treatment. Two years later, a second drug safety communication was published highlighting an addition to the black box warning regarding

reports of worsening symptoms in patients with myasthenia gravis treated with drugs in this therapeutic class. In 2013, this labeling change was again updated to include the risk for irreversible peripheral neuropathy.

In November 2015, an FDA Advisory Committee met to discuss the risks and benefits of fluoroquinolones in the routine treatment of acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and uncomplicated UTIs.[16] The committee concluded that the risk for serious adverse effects outweighed the benefit in these infections and recommended that labeling reflect this information. On May 12, 2016, the FDA issued a drug safety communication to relay the Advisory Committee's findings. This communication also highlighted a recent FDA safety review which found that serious adverse effects involving tendons, muscles, joints, as well as peripheral neuropathy and central nervous system adverse effects could occur within the same patient. In the cases of multiple adverse effects occurring in the same patient that had been reported to the FDA, symptoms occurred within hours to weeks after starting treatment and lasted for an average of 14 months, with the longest duration being 9 years.

On July 26, 2016, a subsequent drug safety communication updated prescribers that the new labeling changes had been implemented.[17] The following November, the American Academy of Pediatrics published a Clinical Report on the use of systemic and topical fluoroquinolones to call attention to the FDA recommendations.[17] The authors, writing for the Committee on Infectious Diseases, noted that while injury to developing bones or joints has not turned out to be a significant risk, the safety reviews conducted by the FDA suggest an increased risk for musculoskeletal adverse events.

The most recent FDA drug safety communication on fluoroquinolones was issued on July 10, 2018 to notify healthcare providers of its intention to strengthen current warnings in the prescribing information of all fluoroquinolones regarding the risk for clinically significant hypoglycemia and mental health adverse effects.[3] While the labeling of most of the fluoroquinolones already contained a warning that blood sugar disturbances, including high blood sugar and low blood sugar, could occur with their use, this new communication highlighted the potential severity of these reactions, including a specific description of the risk for hypoglycemic coma.

The section on mental health adverse effects was made more prominent by separating it from the warnings on central nervous system adverse effects and the language was made consistent across the therapeutic class. The specific mental health adverse effects added to or updated included:

- disturbances in attention
- disorientation
- agitation
- nervousness
- memory impairment
- delirium

Pediatric Adverse Reaction Data

The safety profile of ciprofloxacin was studied by Bayer in an international multicenter trial.[4] A total of 684 children (mean age 6 $\pm$ 4 years, range 1 to 17 years) with a complicated UTI or pyelonephritis were enrolled; 335 received ciprofloxacin and 349 were given a comparator cephalosporin for a mean duration of 11 days (range 1-88 days). The presence of musculoskeletal or neurologic adverse reactions was assessed at 6 weeks and 1 year after treatment and reviewed by an independent pediatric safety committee.

Musculoskeletal adverse reactions included arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg, arm, or back pain, bone pain, myalgia, or decreased range of motion in an ankle, knee, hip, wrist, elbow, or shoulder. The rates of musculoskeletal adverse reactions reported within 6 weeks after the initiation of treatment were 9.3% (31/335) in the ciprofloxacin group and 6% (21/349) in the comparator group (95% CI -0.8%, 7.2%). All signs and symptoms in these patients resolved, most within 1 month of the report. The rates of musculoskeletal adverse effects reported at any point up to 1 year after initiation of treatment were 13.7% (46/337) in the ciprofloxacin group and 9.5% (33/349) in the comparators (95% CI -0.6%, 9.1%). The study was designed to demonstrate that the rate of musculoskeletal adverse reactions for ciprofloxacin did not exceed that of the comparator by more than 6%. At both 6-week and 1-year assessments, it could not be concluded that the ciprofloxacin group had findings similar to the comparator group.

The incidence of neurologic adverse reactions at the 6-week assessment was 3% (9/355) in the ciprofloxacin group and 2% (7/349) in the comparator group. The reactions reported included dizziness, nervousness, insomnia, and somnolence. Overall, the incidence of adverse reactions was 41% in the ciprofloxacin group and 31% in the comparator group, with the most common reactions being gastrointestinal (15% and 9%, respectively). Serious adverse reactions were uncommon, occurring in 7.5% and 5.7% of patients.

Additional adverse reaction data were obtained from a randomized, double-blind trial of 129 patients (6-17 years of age) with cystic fibrosis having an acute pulmonary exacerbation. Patients received either ciprofloxacin or the combination of ceftazidime and tobramycin intravenously for

10-21 days. Symptoms were evaluated for an average of 23 days after completing therapy (range 0-93 days). Musculoskeletal adverse reactions were reported in 22% of the patients in the ciprofloxacin group and 21% of the comparator group.

Several other case reports and case series have described fluoroquinolone adverse effects in children and young adults. Moffett and colleagues described two cases of ciprofloxacin-associated renal insufficiency.[18] Both patients had cystic fibrosis and were being treated for a pulmonary exacerbation. Symptoms began at 10 days and 3 weeks, with a rise in creatinine and blood urea nitrogen. Renal function improved rapidly after discontinuation, with complete resolution within 3 weeks. In the study by Sideri describing ciprofloxacin use in 18 critically ill children, the authors reported two cases of diarrhea, one case of vomiting, and one case of transient supraventricular tachycardia attributed to treatment.[8] The authors found no cases of QT prolongation. In contrast, the authors of the systematic review of ciprofloxacin use in neonates described earlier found no reports of serious adverse effects, but noted that the focus of most of the papers reviewed was on clinical cure and included only limited follow-up.[9]

In a paper just released on-line in *The Journal of Pediatrics*, Shah and Ong described an 8-year-old child who developed an erythematous rash and superficial venous thrombophlebitis after being given a single IV ciprofloxacin dose for nephrostomy tube replacement.[19] His symptoms resolved within a few hours. This was felt to be a local reaction and he was subsequently given a 10-day course of oral ciprofloxacin without adverse effects.

Summary

The use of ciprofloxacin in infants and children requires careful consideration. While still a very useful option for patients with multidrug resistant infections susceptible to a fluoroquinolone, it should no longer be considered first-line therapy for uncomplicated infections. Growing concerns over bacterial resistance and the risk for serious, sometimes irreversible adverse effects, now limit its use to only those patients with no safer alternatives.

References

1. Ciprofloxacin. Drugs@FDA: Food and Drug Administration approved drug products. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019537 (accessed 7/28/18).
2. Linder JA, Huang ES, Steinman MA, et al. Fluoroquinolone prescribing in the Unites States: 1995-2002. Am J Med 2005;118:259-68.
3. Food and Drug Administration. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. July 10, 2018. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm612979.htm (available 7/28/18).
4. Cipro® prescribing information. Bayer Healthcare Pharmaceuticals, Inc. July 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019537s087,020780s044lbl.pdf (accessed 7/28/18).
5. Etminan M, Guo M, Carleton B. Oral fluoroquinolone prescribing to children in the United States from 2006 to 2015. Pediatr Infect Dis J 2018; May 24. doi 10.1097/INF.0000000000002121. [Epub ahead of print].
6. Jackson MA, Schutze GE, American Academy of Pediatrics Committee on Infectious Diseases. The use of fluoroquinolones. Pediatrics 2016;138:e20162706.
7. Meesters K, Mauel R, Dhont E, et al. Systemic fluoroquinolone prescriptions for hospitalized children in Belgium, results of a multicenter retrospective drug utilization study. BMC Infect Dis 2018;18:89. doi: 10.1186/s12879-018-2994-z.
8. Faghihi T, Tekmehadash LY, Radfar M, et al. Ciprofloxacin use in hospitalized children: approved or off-label? J Res Pharm Pract 2017;6:193-8.
9. Sideri G, Kafetzis DA, Vouloumanou EK, et al. Ciprofloxacin in critically ill children. Anaesth Intensive Care 2011;39:635-9.
10. Bannon MJ, Stutchfield PR, Weindling AM, et al. Ciprofloxacin in neonatal Enterobacter cloacae septicemia. Arch Dis Child 1989;64:1388-91.
11. Kaguelidou F, Turner MA, Choonara I, et al. Ciprofloxacin use in neonates: a systematic review of the literature. Pediatr Infect Dis J 2011;30:e29-e37.
12. Conley ZC, Bodine TJ, Chou A, et al. Wicked: the untold story of ciprofloxacin. PLoS Pathog 2018;14:e1006805.
13. Rose L, Coulter M, Chan S, et al. The quest for the best metric of antibiotic use and its correlation with the emergence of fluoroquinolone resistance in children. Pediatr Infect Dis J 2014;33:e158-e161.
14. Saksena R, Gaind R, Sinha A, et al. High prevalence of fluoroquinolone resistance amongst commensal flora of antibiotic naïve neonates: a study from India. J Med Microbiol 2018;67:481-8.
15. Karp BE, Campbell D, Chen JC, et al. Plasmid-mediated quinolone resistance in human non-typhoidal Salmonella infections: an emerging public health problem in the United States. Zoonoses Public Health 2018 July 19; doi: 10.1111/zph.12507.
16. Food and Drug Administration. FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. May 12, 2016. Available at www.fda.gov/Drugs/DrugSafety/ucm500143.htm (accessed 7/28/18).
17. Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. July 26, 2016. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm (accessed 7/28/18).
18. Moffett BS, Rosentein BJ, Mogayzel PJ. Ciprofloxacin-induced renal insufficiency in cystic fibrosis. J Cystic Fibrosis 2003;2;152-4.
19. Shah A, Ong PY. Immediate superficial venous thrombophlebitis associated with intravenous administration of ciprofloxacin. J Pediatr 2018; doi: 10.1016/j.jpeds.2018.03.045. [Epub ahead of print].