Will Fluoroquinolones Ever Be Recommended for Common Infections in Children?

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In this issue of *The Pediatric Infectious Disease Journal*, there are 2 articles reporting efficacy and safety experiences with levofloxacin in children.[1,2]

This commentary attempts to summarize the actual knowledge and guidelines for the systemic use of fluoroquinolones in children, and to bring into perspective the new data.

BACKGROUND

Many of the characteristics of the contemporary fluoroquinolones, the derivatives of the first quinolone antibiotic, nalidixic acid, are particularly appealing for certain pediatric populations. The fluoroquinolones are rapidly bactericidal and have an extended antimicrobial spectrum that includes *Pseudomonas*, Gram-positive cocci, and intracellular pathogens. They have advantageous pharmacokinetic properties such as absorption from the gastrointestinal tract, excellent penetration into many tissues, and good intracellular diffusion. These antimicrobials have been effective in the treatment or prevention of a variety of bacterial infections in adults, including infections of the respiratory and urinary tracts, skin and soft tissue, bone and joint, and eye and ear. Overall, fluoroquinolones are generally well tolerated; the most frequent adverse events during treatment are gastrointestinal disturbances, reactions of the central nervous system, and skin reactions.[3]

The use of fluoroquinolones in children has been limited because of their potential to induce arthropathy in juvenile animals.[4–6] Besides feared arthrotoxicity, the second major concern regarding use of fluoroquinolones in children is the potential development of bacterial resistance.[7]

QUINOLONE ARTHROPATHY

All quinolones tested, including the older compounds and the newer derivatives, induce changes in immature cartilage of weight-bearing joints in all laboratory animals tested (mice, rats, dogs, marmosets, guinea pigs, rabbits, and ferrets).[3,5,6,8] Quinolone-induced arthropathy is limited to juve-nile animals, except when pefloxacin has been used. Juvenile dogs are generally more sensitive to the arthropathic effects of quinolones than are other species. Healing of quinolone-induced arthropathy is incomplete—even after complete clinical recovery; structural changes are, at least in part, irreversible.

When clinically manifested in exposed animals, the quinolone-induced joint lesions present as acute arthritis, including limping and swelling. The specific mechanism responsible for the initiation of quinolone-induced arthropathy has not been determined. At present, inhibition of mitochondrial DNA replication[9] and the role of magnesium deficiency[10] are the most discussed hypotheses.

Neither pharmacokinetic nor pharmacodynamic data can explain the variable arthropathic effect of different compounds in animal experiments. There is also no clear effect of the molecular structure of the given compound, regarding its cartilage toxicity (eg, quinolones that are fluorinated versus quinolones that are not fluorinated).

The available methods for monitoring for quinolone-induced cartilage toxicity are the following:

Histopathology—the standard.[11]

Magnetic resonance imaging—the profiles are surface, thickness, and structure of cartilage; presence of effusion (especially recessus suprapatellaris); and bone/cartilage integrity.[12–15]

Sonography—measurement includes presence/absence of effusion, and thickness and surface of cartilage.[13–15]

Clinical examination—indicating symptoms and signs would be arthralgia, limping, and joint-swelling, and for long-term follow-up, growth rate; in many animal experiments, cartilage toxicity, was documented, however, without any clinical manifestation.

Comprehensive reviews of published reports including monitoring for quinolone-induced cartilage toxicity in patients were performed.[16,17] The reviewed studies included all case reports of suspected quinolone-associated arthralgia/arthropathy in children and adolescents, and all multipatient studies on the use of quinolone compounds in skeletally immature patients (open-label and controlled trials) in which there were data on safety, especially regarding potential arthropathy. Most of the data were based on clinical findings—musculoskeletal complaints and joint examination. Such findings do not allow one to distinguish between coincidental joint problems and quinolone-induced arthropathy. Magnetic resonance imaging, ultrasonography, and growth curve have been rarely used for either short-term or long-term evaluation. With the exception of the findings in 2 cystic

fibrosis patients,[11] the standard index of histopathology is lacking. There are 4 conclusions:

To date there is no unequivocal documentation of quinolone-induced arthropathy in patients as described in juvenile animals; quinolone arthropathy remains an experimental laboratory phenomenon in juvenile animals.

Clinical observations temporally related to quinolone use are reversible episodes of arthralgia with and without effusions that do not lead to long-term sequelae when treatment with the agents is discontinued.

Most joint complaints associated with quinolone use are coincidental and do not represent adverse effects. Possible coincidental conditions include arthropathy and hypertrophic pulmonary osteoarthropathy associated with cystic fibrosis,[18] and reactive, traumatic and rheumatic joint diseases.

It is postulated that the so-called allergic arthritis initially described in nalidixic acid-treated patients does exist, but is not the same as the quinolone-induced arthropathy in animals. These adverse events are always transient arthralgic or arthritic manifestations, usually involving large joints and occurring during the first and second week of therapy. The overall incidence is 1% to 3% (-18%) depending on the studied patient group and quinolone compound.

BACTERIAL RESISTANCE

There is great concern regarding the potential impact of widespread fluoroquinolone use in children on bacterial resistance development.[7,8,19–21]

Historically, antimicrobial use has led to the development of drug resistance. The relevant drivers are overuse (volume of antibiotic used in humans and in animals), misuse (inappropriate use), clonal spread (global travel, hygiene, hospital, daycare, family, switch of serotypes), and type of antibiotic.

Evidence is accumulating that multidrug resistance in pneumococci is related to prescription of antimicrobial agents to a crucial reservoir of these organisms—children. This multidrug resistance likely occurs because children, more often than adults, are colonized with high-density populations of pneumococci in the nasopharynx, which increases the potential for resistance development.[19] Overcrowding facilitates the transmission of resistance strains from colonized to susceptible infants and children, who serve as a source for further transmission to family members and ultimately to the general population.[22]

EXPERIENCES IN PEDIATRIC PATIENTS

Since the mid-1980s, fluoroquinolones have been used in pediatric patients primarily in circumstances where they were the only antimicrobial choice for infections caused by multiply-resistant organisms. These included pseudomonal infections in children with cystic fibrosis, complicated urinary tract and skeletal infections, enteric infections in developing countries, and ear infections, both chronic suppurative otitis media and refractory acute otitis media. Results of controlled clinical trials in patients with these indications have shown comparable efficacy of the fluoroquinolones and conventional regimens.[7,17,23] Preliminary experience in pediatric patients also indicates that the fluoroquinolones are effective and safe for the prevention or therapy for infections in neutropenic cancer patients, for the eradication of nasopharyngeal carriage of meningococci and for therapy for severe infections, including meningitis.

"NEW" DATA ON LEVOFLOXACIN?

The first study by Bradley and colleagues[1] confirms efficacy and safety of levofloxacin for community-acquired pneumonia in children—as previously established in adult patients. This trial was conducted at 43 centers in 7 countries, only 36% of 539 children available for clinical/radiologic evaluation were diagnosed with a specific etiology at admission to the trial, and no respiratory viruses were routinely searched for. It is likely that patients with viral lower respiratory tract infections were included. Whenever feasible, every diagnostic effort should be undertaken to identify reliably children with pneumonia who really need antibiotic therapy. This study certainly should not be cited as basis for unrestricted use of levofloxacin for treatment of pediatric community-acquired pneumonia.

The second study summarizes safety data recorded during and after 3 pediatric efficacy trials of levofloxacin, with emphasis on musculoskeletal disorders.[2] No typical quinolone-induced joint toxicity as described in laboratory animals was found. Musculoskeletal events observed in 3.3% of levofloxacin- and in 2.6% of comparator-treated patients (first database from the 3 efficacy trials) up to 1 month posttherapy indicate transient arthralgic or arthritic manifestations potentially related to levofloxacin in 1.6%, and to comparator antibiotics in 1.0%. The authors attempt to correlate musculoskeletal events reported by unblinded patients/parents between 1 and 12 months posttherapy with levofloxacin use (second database from 12-month observation trial). The incidence of all reported musculoskeletal events were similar for levofloxacin- and comparator-treated children: 7.8% versus 5.6%. All events were reversible and only very few of these events classified as musculoskeletal disorders were supported by objective clinical findings, 4 of 49 = 8.2% in the levofloxacin, and 1 of 17 = 5.9% in the comparator group. The hypothesis to correlate these vague, nonspecific, and not objectively documented, reversible musculoskeletal events with any drug administered 1 to 12 months before cannot be supported.

CONCLUSION

The 2 major concerns regarding use of fluoroquinolones in children are development of bacterial resistance and cartilage toxicity as described in juvenile animals. The risk for rapid emergence of resistance among pneumococci and other common bacterial pathogens, associated with widespread, uncontrolled use of fluoroquinolones in pediatric patients, is a realistic threat. Cartilage toxicity with fluoroquinolones is a laboratory phenomenon in juvenile animals, and no arthropathy has been documented unequivocally in the large numbers of children

treated with these agents. Nevertheless, expectant observation is warranted for any new quinolone use in pediatrics.

Based on available data showing the safety and efficacy of the fluoroquinolones, selected pediatric patients should not be deprived of the therapeutic advantages that these agents have to offer. The quinolones should not be used in pediatric patients for routine treatment when alternative safe and effective antimicrobials are available. To date, established pediatric indications for the fluoroquinolones include bronchopulmonary exacerbation in cystic fibrosis, complicated urinary tract and skeletal infection, invasive gastrointestinal infection, and chronic ear infection. Potential pediatric indications are sepsis including bacterial meningitis, and refractory acute otitis media.

In most countries, fluoroquinolones have been approved for use only in pediatric patients with cystic fibrosis and complicated urinary tract infection. Authorization for broader use of new fluoroquinolones in children must combine efforts of experts in infectious diseases and microbiology, regulatory authorities, and pharmaceutical manufacturers. Postmarketing surveillance must include an adequate risk management plan feasible for patients, parents, and drug companies.

Will fluoroquinolones ever be recommended for common infections in children? The triad of feared arthrotoxicity, potential resistance explosion, and enormous requirements regarding adequate study and postmarketing control suggests that the answer is no.

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