

PEDIATRICS

Do fluoroquinolones commonly cause arthropathy in children?

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ABSTRACT

Objective: The objective of this paper was to review the relation between fluoroquinolone (FQ) use and arthropathy in children.

Methods: The biomedical literature from January 1980 to February 2007 was searched using PubMed. Key search terms included fluoroquinolones, arthropathy, tendinopathy and children. Literature was included if it was a clinical trial or meta-analysis examining the use of 1 or more FQs in a pediatric human population and if it had a primary outcome measure of reported incidence of arthropathy or tendinopathy. Articles were excluded if the primary outcome measure was efficacy of an FQ in a particular pediatric disease state, and evaluated safety was a secondary end point.

Results: Data was reviewed from 4 large retrospective studies. Three of the 4 studies failed to find a significant link between musculoskeletal injury and FQ treatment. One study reported a correlation between use of pefloxacin and arthropathy, but the authors' conclusions supported the use of FQs in select pediatric cases.

Conclusion: Arthropathy that occurs as a result of FQ use in children has not been adequately supported by published data from safety trials in human children. Concerns about arthropathy with FQs should not preclude their use by emergency physicians when appropriate and necessary in pediatric patients.

Key words: fluoroquinolones, tendinopathy, adverse effects, pediatrics

RÉSUMÉ

Objectif : Cette communication visait à étudier le lien entre l'utilisation de fluoroquinolones (FQ) et l'arthropathie chez les enfants.

Méthodes : On a effectué des recherches dans les publications biomédicales de janvier 1980 à février 2007 au moyen de PubMed. Les thèmes de recherche clés ont inclus les mots *fluoroquinolones*, *arthropathy*, *tendinopathy* et *children*. On a inclus les publications s'il s'agissait d'une étude clinique ou d'une méta-analyse portant sur l'utilisation d'une FQ ou plus dans une population humaine pédiatrique et si l'étude comportait, comme principale mesure de résultat, l'incidence déclarée d'arthropathie ou de tendinopathie. On a exclu les articles si la mesure principale de résultat portait sur l'efficacité d'une FQ pour un état morbide pédiatrique particulier et si l'innocuité évaluée constituait un point final secondaire.

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Received: Dec. 5, 2006; revisions received: Feb. 24, 2007; accepted: Mar. 12, 2007

This article has been peer reviewed.

Can J Emerg Med 2007;9(6):459-62

Résultats : On a analysé les données tirées de quatre études rétrospectives d'envergure. Trois des quatre études n'ont pas révélé de lien significatif entre des lésions musculosquelettiques et le traitement aux FQ. Une étude a signalé un lien entre l'utilisation de pefloxacin et l'arthropathie, mais les conclusions de l'auteur ont appuyé l'utilisation de FQ dans certains cas pédiatriques.

Conclusion : Les données publiées découlant d'études d'innocuité chez des enfants humains n'ont pas démontré adéquatement que l'utilisation de FQ chez les enfants entraîne une arthropathie. Les préoccupations soulevées au sujet de l'arthropathie causée par les FQ ne devraient pas empêcher les médecins d'urgence de les utiliser au besoin lorsque la situation l'exige chez les patients en pédiatrie.

Introduction

Since their introduction into clinical use, fluoroquinolones (FQs) have become an integral part of our antimicrobial armamentarium. They have a broad spectrum of activity, especially the newer agents, which makes them useful in treating numerous infectious diseases. Emergency physicians may encounter pediatric patients with severe infections that would, if the patient were an adult, be typically treated with an FQ. Drug allergies, increasing antimicrobial resistance and the relative lack of new antibiotics reduce the treatment options for difficult infections in children. In these uncommon but serious circumstances, emergency physicians may need to consider using an FQ. The greatest concern about using this class of drugs in children stems from the historical perception that FQs pose a high risk for arthropathy in these patients.

Shortly after nalidixic acid was first marketed for pediatric use in the 1960s, safety concerns arose when case reports suggested a link with arthropathy in children. One of the first cases involved a child who developed soreness in the wrist following a course of nalidixic acid.¹ Other similar case reports prompted further experimentation on laboratory animals. Changes were noted in the immature cartilage of weight-bearing joints in all animal species (mice, rats, dogs, marmosets, guinea pigs, rabbits and ferrets) studied after exposure to various FQs. Histological samples showed lesions that ranged from fluid-filled blisters, fissures and erosions, to synovial inflammation.^{2,3} Electron microscopy revealed chondrocyte necrosis and loss of collagen and glycosaminoglycan in some animal studies.³ Pathophysiologic mechanisms for the arthropathy were not determined, but postulated mechanisms include FQ-induced oxidative injury or chelation of magnesium ions leading to destabilization of joint cartilage.³

Age was determined to be the most important factor in the development of FQ arthropathy in animals, and rapid growth rate appeared to be important. Dogs have comparable FQ pharmacokinetics to humans, and beagle puppies

demonstrated significant arthropathy when exposed to nalidixic acid doses lower than the 55 mg/kg then approved for children.³ With limited human data on which to depend, some authors speculated that the growth of a puppy during its first year might be comparable to the growth of a child during the first 18 years of life, and that these drugs might therefore pose significant risk to children.³

Although general consensus is that FQs may be acceptable for pediatric use under special circumstances, most clinicians avoid oral or intravenous FQs in children since FDA-approved product labelling cautions against their use in this population. This article reviews the literature regarding the association between FQ use in children and the occurrence of arthropathy or tendinopathy.

Methods

A PubMed search of English-language literature from January 1980 to February 2007 was performed combining the search terms fluoroquinolones, arthropathy, tendinopathy and children. Literature was included if it was a clinical trial or a meta-analysis examining the use of 1 or more FQs in a pediatric human population that had a primary outcome measure of reported incidence of arthropathy or tendinopathy. Review articles identified in this search were also examined for pertinent historical information, and the references of all articles were examined for additional clinical trials that met inclusion criteria. To narrow the scope of the search and to evaluate the best evidence possible, studies of FQs in children were excluded if the primary outcome measure was the clinical efficacy of the drug in a particular disease state and safety analysis was a secondary outcome.

The literature

The occurrence of arthropathy in children has been the primary end point evaluated in several large retrospective studies. In a comprehensive review of 7045 patients

described in 31 studies of skeletally immature patients, the incidence of arthropathy due to ciprofloxacin, norfloxacin, ofloxacin or nalidixic acid was evaluated.³ Ten cases of transient arthralgia were identified, most frequently associated with pefloxacin, but no single case could be directly attributable to FQ therapy. The studies used diverse methods of follow-up (i.e., magnetic resonance imaging, clinical evaluation, radiography, ultrasonography and histopathology) and reported normal skeletal growth at a range of 1 week to 12 years after treatment. Based on these data, the authors calculated with 95% confidence that the risk of chondrotoxicity was less than 1 in 2348 patients or 0.04%. Limitations to this study include the fact that there was no mention of an assessment of the 31 included studies for publication bias as well as the fact that the authors did not provide subgroup analyses where it may have been appropriate in the presence of heterogeneity of the study populations.

In France, investigators used a multi-centre, non-blinded cohort study design to assess adverse events in children who received ciprofloxacin or pefloxacin.⁴ Data were gathered from 145 pediatric centres comparing children who received an FQ with a control group who received non-FQ antibiotics. Indications for antibiotic prescriptions were broken down into subgroups. In the FQ group, patients with cystic fibrosis (CF) were treated for active bronchopulmonary infections (93%), bronchopulmonary infection prophylaxis (4%) and sinusitis (2%). Patients without CF were treated for bronchopulmonary infections (22%); urinary tract infections (18%); febrile neutropenia (13%); septicemia (12%); *Salmonella* or *Shigella* gastrointestinal tract infections (12%); ear, nose and throat infections (6%); bone or joint infections (6%); and meningitis (5%). Indications among children receiving a non-FQ antibiotic were similar, with the exceptions of more frequent febrile neutropenia (22%, $p = 0.03$) and less frequent *Salmonella* or *Shigella* gastrointestinal tract infections (5%, $p = 0.01$), septicemia (4%, $p = 0.003$) or meningitis (0%, $p = 0.001$).

Of the 276 FQ recipients, 264 were evaluated after 15 days observation and 52 potential adverse events were reported, 10 involving the musculoskeletal system, including large joint arthralgias and myalgias — but no tendinopathy. In the control group of 249 patients, 237 were evaluated at follow-up, and only 1 potential musculoskeletal adverse event was documented. A crude odds ratio for musculoskeletal potential adverse events in the FQ group was 9.3 (95% confidence interval [CI] 1.2–195, $p = 0.02$). When adjusted for age, underlying conditions, exposure to FQ within 5 years and number of concomitant drugs, the odds ratio for all potential adverse events in the FQ group was 3.0 (95%

CI 1.5–5.9, $p = 0.002$). In this study, musculoskeletal events were more common with pefloxacin than ciprofloxacin (18.2% v. 3.3%, $p = 0.06$). Of the 10 musculoskeletal events in the FQ group, only 3 required medication discontinuation and all were transient, without long-term sequelae. Despite the suggested link between arthropathy and FQs in this article, the authors' conclusion supported off-label use of FQs as second line therapy in limited situations. An important limitation to this study is that it was nonrandomized and open-labelled. This could potentially have led to a misclassification bias, and an overestimation of musculoskeletal events attributed to FQ use, as children receiving FQs may have been monitored more closely for adverse events and more likely to have them reported if they occurred. Indication could have further confounded the results, as children with more severe disease were generally given FQs despite attempts to match patients.

In a 2004 study, investigators described adverse events in 116 septic neonates who received ciprofloxacin.⁵ When compared with a control group of 100 randomly selected septic neonates matched for gestational age and birth weight who received other antimicrobials, no clinical outcome differences were found and no short-term hematologic, renal or hepatic adverse drug reactions were noted. Clinical arthropathy and growth impairment were not associated with ciprofloxacin use in this study, even at 1 year of follow-up. The use of clinical evaluation to determine the incidence of arthropathy and growth impairment without using supporting evidence from ultrasound or magnetic resonance imaging could be considered a limitation in this study, as neonates would be less likely to communicate joint arthralgias. Diagnosis using clinical evaluation has the potential to vary greatly among the evaluators.

Yee and colleagues⁶ used the United Health Care Research Database to retrospectively study the risk of tendon or joint disorders in patients under 19 years of age who received a quinolone (ofloxacin, levofloxacin or ciprofloxacin) versus azithromycin. Azithromycin was chosen as a comparator because of the large number of patients in the database who had received it. Cases of tendon or joint disorders were identified based on assignment of a claims diagnosis and verified by blinded independent reviews of the medical records. Levofloxacin was not used frequently enough to evaluate its safety, but the verified incidence of tendon or joint disorders was 0.82% (13 of 1593) with ofloxacin, 0.82% (37 of 4531) with ciprofloxacin and 0.78% (118 of 15 073) with azithromycin. The relative risk of tendon or joint disorders with ofloxacin, compared with azithromycin, was 1.04 (95% CI 0.72–1.51); and of ciprofloxacin, compared with

azithromycin, it was 1.04 (95% CI 0.55–1.84). This retrospective study may have overestimated the incidence by relying on a broad range of ICD-9 codes to maximize sensitivity for finding potential tendon or joint disorders. Relatively few children in this study were under 10 years of age, hence the sample size may be insufficient to conclude safety in this subgroup.

Limitations

Adverse drug effects are under reported in published literature, so it is possible that the real risk of FQ arthropathy is higher than how it is described in the studies we reviewed. Another possible limitation of this review was our search strategy, which included only articles that used arthropathy as a primary outcome and excluded studies that used FQ efficacy as a primary end point. Of note, an exploratory evaluation of several efficacy studies suggests that these identify a similarly weak association between FQ use and arthropathy; therefore, we believe our search strategy does not compromise our conclusions.

Discussion

Case reports and animal studies have identified a potential relation between FQ use and arthropathy in children. While this has appropriately limited the use of these antibiotics, published literature suggests that the risk of arthropathy in children treated with quinolones is very low. The most common concern associated with FQ use is transient reversible arthralgia, and many of the joint complaints reported in prior studies were coincidental — not necessarily representative of actual adverse drug events. Prospective studies are usually too small to evaluate rare (safety) outcome events, so much of the information must be evaluated through analyses of retrospective data like that discussed in this article. While such data are limited, they suggest that the relation between fluoroquinolones and the development of pediatric arthropathy is tenuous and not sufficient to recommend avoiding their use in children when the benefit clearly outweighs the risk.

Currently, fluoroquinolones are reserved for use in children with life-threatening or difficult-to-treat infections, or when other antibiotics are contraindicated because of drug allergy, drug toxicity or antimicrobial resistance.⁷ Examples of appropriate use include exacerbations of CF, uri-

nary tract infections caused by multi-drug resistant gram-negative bacteria or persistent otitis media that has become refractory to conventional antibiotics. Such patients are likely to present to emergency departments when access to a primary care physician or pediatrician is limited.

Conclusion

Although the association between quinolones and pediatric arthropathy is weak, it is prudent to initiate less controversial antibiotics when appropriate. Treatment decisions should be based on factors such as the severity of infection, the history of infections and previous antibiotics used, and local antibiotic sensitivity patterns. When quinolones are prescribed for children, clinicians should monitor closely for symptomatic arthralgias; however, concerns about arthropathy should not preclude their use in the ED when appropriate and necessary.

Competing interests: None declared.

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