Ciprofloxacin safety in paediatrics: a systematic review

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ABSTRACT

Objective To determine the safety of ciprofloxacin in paediatric patients in relation to arthropathy, any other adverse events (AEs) and drug interactions.

Methods A systematic search of MEDLINE, EMBASE, CINAHL, CENTRAL and bibliographies of relevant articles was carried out for all published articles, regardless of design, that involved the use of ciprofloxacin in any paediatric age group ≤17 years. Only articles that reported on safety were included.

Results 105 articles met the inclusion criteria and involved 16 184 paediatric patients. There were 1065 reported AEs (risk 7%, 95% CI 3.2% to 14.0%). The most frequent AEs were musculoskeletal AEs, abnormal liver function tests, nausea, changes in white blood cell counts and vomiting. There were six drug interactions (with aminophylline (4) and methotrexate (2)). The only drug related death occurred in a neonate who had an anaphylactic reaction. 258 musculoskeletal events occurred in 232 paediatric patients (risk 1.6%, 95% CI 0.9% to 2.6%). Arthralgia accounted for 50% of these. The age of occurrence of arthropathy ranged from 7 months to 17 years (median 10 years). All cases of arthropathy resolved or improved with management. One prospective controlled study estimated the risk of arthropathy as 9.3 (OR 95% CI 1.2 to 195). Pooled safety data of controlled trials in this review estimated the risk of arthropathy as 1.57 (OR 95% CI 1.26 to 1.97).

Conclusion Musculoskeletal AEs occur due to ciprofloxacin use. However, these musculoskeletal events are reversible with management. It is recommended that further prospective controlled studies should be carried out to evaluate the safety of ciprofloxacin, with particular focus on the risk of arthropathy.

What is already known on this topic

- Ciprofloxacin is a broad spectrum, bactericidal antibiotic with good tissue penetration.
- Ciprofloxacin and fluoroquinolones as a group, cause arthropathy in weight bearing joints of juvenile animals.
- The use of ciprofloxacin in paediatrics has been limited due to the possibility of arthropathy.

What this study adds

- Musculoskeletal adverse events (AEs) are the most frequently reported AEs in paediatric patients after ciprofloxacin use.
- All musculoskeletal AEs reported in the literature have been reversible following withdrawal of ciprofloxacin.

INTRODUCTION

The first quinolone discovered was nalidixic acid in 1962, as a by-product of antimalarial research. Its use was limited due to its narrow spectrum of antibacterial activity, low serum levels and toxicity issues.[1] Fluorination of the quinolone nucleus at position 6 resulted in introduction of second, third and fourth generations of fluoroquinolones, with ciprofloxacin in 1987 as a second generation fluoroquinolone.[2] Ciprofloxacin is a broad spectrum, bactericidal antibiotic which acts by binding two of the four topoisomerases of bacteria.[3]

The use of ciprofloxacin and fluoroquinolones as a group in paediatric patients has been limited due to arthropathy noticed in weight bearing joints of juvenile animals. Cartilage damage caused by quinolones (nalidixic, oxolinic and pipemidic acids) was first reported in juvenile animals (beagle dogs 4–12 months of age).[4] The arthropathy caused by quinolones has also been demonstrated in other animal species such as mice,[5] dogs,[6] rats[7] and rabbits,[8] and in in-vitro animal culture[9] and in-vitro human cell culture.[10]

Due to the good antibacterial activity and tissue penetration, different investigators have used ciprofloxacin in paediatric patients. The occurrence of arthropathy is uncertain. Other adverse drug reactions and drug interactions have been reported with ciprofloxacin use in adults.[11] However, the drug toxicity profile has not been ascertained in paediatric use. This systematic review aims to pool together all the safety data about use of ciprofloxacin in paediatrics, with a critical look at the occurrence of arthropathy.

METHODS

Search strategy

We searched MEDLINE (1950 to November 2009), EMBASE (1950 to November 2009), the Cochrane database for systematic reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for any study with documented involvement of any paediatric age group (0–17 years) that used ciprofloxacin as intervention via any route of administration and for any disease condition. There was no restriction on the type of study that was included, language of publication or inclusion of abstracts. Any study with involvement of a paediatric age group participant taking at least a single dose of ciprofloxacin was included. This was necessary to

ascertain the extent of use of ciprofloxacin in paediatrics and to be able to pool any documented adverse events (AEs) involving any paediatric age group. Hand searching of references of articles was also done. Studies that involved only adults were excluded. Search terms comprised both subject headings and free text words. These included terms relating to ciprofloxacin or quinolones or fluoroquinolones; adverse effects or adverse drug reactions or side effects; arthropathy or cartilage toxicity or chondrotoxicity or joint damage; and pharmacokinetics (see online supplementary appendix 1).

Outcome measures

The prespecified outcomes were as follows:

1. Occurrence of arthropathy specified as joint pain, joint swelling, reduced movement of joint or radiographic evidence of joint damage and any other musculoskeletal AE.
2. Occurrence of any other AEs from ciprofloxacin use.
3. Occurrence of drug–drug interactions due to ciprofloxacin use.
4. Death due to adverse drug reaction from ciprofloxacin use.

Data collection and analysis

The relevant data were extracted onto the data extraction form. Only studies that reported on the number of paediatric patients within each study and reported on safety of ciprofloxacin in the paediatric patients were analysed. Participants in the study were grouped into the following paediatric age groups: preterm neonates (<36 weeks gestation, 0–27 days); full-term neonates (0–27 days, >37 weeks gestation); infants and toddlers (28 days to 23 months); children (2–11 years); and adolescents (12–17 years). AEs were classified according to the WHO adverse reaction terminology classification into one of the several organ systems, and were further analysed to determine which AEs actually occurred in any of the paediatric age groups (see online supplementary appendix 2). The arthropathy reports were analysed for causality in relation to the time of exposure to the drug, presence of other disease and medications.[12] Details of the arthropathy included the time to development of arthropathy following ciprofloxacin use; the time to follow-up of patients after use of ciprofloxacin; method of detecting arthropathy in patients; and any management of the arthropathy. A descriptive analysis of extracted data was performed. Statistical analysis was carried out using SPSS V.18 and GraphPad software.

RESULTS

We identified a total of 105 studies (figure 1), the majority of which were case series or case reports[13–117] (table 1). However, most of the patients (88%) were within case series or cohort studies.

Dosage and formulations

The dose ranged from 3.1 to 93.8 mg/kg/day (oral) and 3.2 to 76.9 mg/kg/day (intravenous).[68] The usual dose in at least 60% of studies was 10–30 mg/kg/day in two divided doses for both oral and intravenous administration. The duration of ciprofloxacin ranged from single dose (pharmacokinetic studies, therapy for cholera and prophylaxis for meningococcal disease) to 880 days (a 12-year-old with osteomyelitis).[68] The median duration of use was 14 days.

Due to the lack of a commercially available paediatric formulation, various formulations were used, including a prepared suspension from granular ciprofloxacin,[16 18 66] tablets,[19 25 44 81 98 115] ground tablets,[82] a suspension formulation from Bayer,[13 22] pulverised tablets with sweet liquid,[42] and tablets crushed and mixed in cherry syrup.[70] Topical ciprofloxacin was administered as drops to the eyes/ears.

Analysis of safety

All reported AEs were analysed together (table 2). Sixty-eight studies reported AEs, while 37 studies reported no AEs. In total, 16 184 paediatric patients were exposed to ciprofloxacin and there were 1065 reported AEs. This gave an estimated risk of 7 AEs in every 100 patients (7%, 95% CI 3.2% to 14.0%), or 1 AE in every 14 patients receiving ciprofloxacin.

The most frequent AEs were musculoskeletal problems, abnormal liver function tests, nausea, changes in white blood cell counts and vomiting (table 2). These are pooled safety data of reported AEs by individual authors of the studies in our review. There was no dose dependent or duration dependent risk of toxicity.

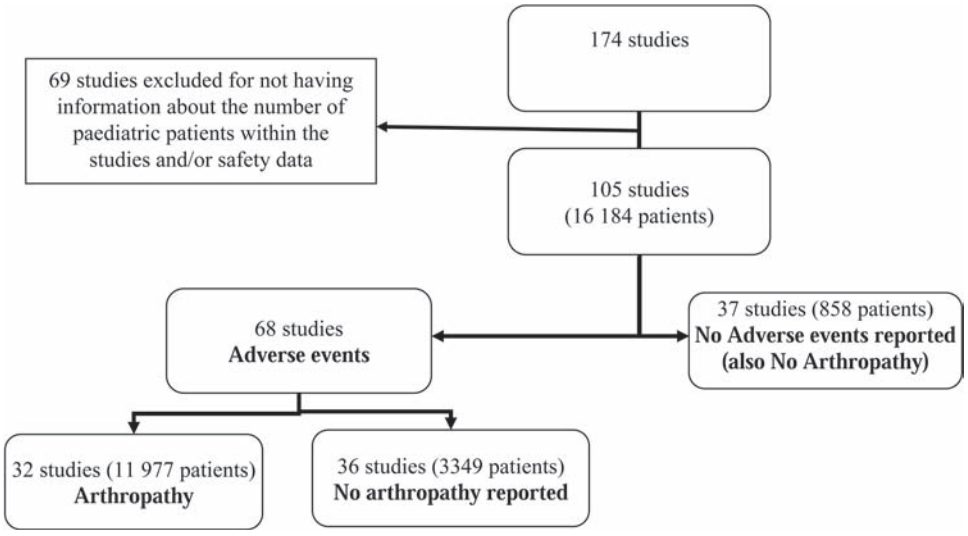

Figure 1 Algorithm of the analysis of the studies in the systematic review.

Table 1 Summary of 105 studies that reported on safety of ciprofloxacin in paediatrics

Type of study	Frequency (N=105)	Number of patients (N=16 184)
Case series	46	8876
Case report	24	24
RCT	15	1787
Cohort study	12	5368
Pharmacokinetic	5	79
Non-RCT	3	50
Route of administration	**Frequency (N=105)**	**Number of patients (N=16 184)**
Oral	39	1871
Intravenous	25	329
Intravenous and oral	19	6489
Not reported	16	6905
Topical	6	590
Age group	**Frequency (N)***	**Number of patients†**
Children	67	NA
Adolescents	53	NA
Infants	40	NA
Preterm neonates	19	NA
Neonates (GA not stated)	18	NA
Term Neonates	9	NA

*Total number of studies for age group is not 105 studies because multiple age groups were included within some studies.
†The number of patients in each age group could not be ascertained because most studies involved more than one age group and the number within each age group was not reported.
GA, gestational age; NA, not available; RCT, randomised controlled trial.

Table 2 Summary of reported adverse events (AEs) from 68 studies

AEs	Frequency
Musculoskeletal	232*
Abnormal liver function tests	139
Nausea	75
Blood cell count derangements	57
Vomiting	56
Rash	51
Injection site reaction	47
Headache	41
Hearing/eye associated AEs	42
Abdominal pain/discomfort	38
Diarrhoea	36
Psychiatric disorders	18
Dizziness/decreased consciousness	13
Pruritus	2
Irritability/anxiety/nervousness	12
Photosensitivity	10
Acute renal failure/impaired renal function	9
Abdominal distension	8
Allergy/anaphylactoid reaction	7
Oral cavity abnormalities	6
Bleeding	6
Hemiparesis/hypotonia/hyperreflexia/ataxia	5
Fever/hot flushes	5
Rigors/shivering/tremors	4
Interstitial nephritis	4
Others†	34
Not specified‡	98
Total	1065

*232 patients had 258 musculoskeletal events.
†Others include AEs which occurred once, twice or thrice only. These include seizures, haemolytic uraemic syndrome, pseudomembranous colitis, gastro-oesophageal reflux disease, urinary retention, greenish discolouration of teeth, malaise, weight loss, dysuria, heart failure, sinoatrial nodal arrest and tachycardia.
‡Not specified AEs reported as unknown.

Drug related death occurred in a neonate who experienced an anaphylactic reaction following intravenous ciprofloxacin. An additional 23 paediatric patients had to discontinue ciprofloxacin due to serious AEs (table 3).

There were six drug interactions with ciprofloxacin. Four patients had drug interactions with aminophylline[47] (two patients were irritable/restless, one had tremors and one had hot flushes). Two patients had delayed elimination of methotrexate.[55] However, there was no drug interaction with aminophylline in seven preterm babies.[21]

Arthropathy

Thirty-two studies reported arthropathy, while 73 studies reported no arthropathy (37 studies reporting no AEs + 36 studies of those reporting AEs that reported no arthropathy). There was no evidence that dose or duration had an effect on arthropathy.

In total, 16 184 paediatric patients were exposed to ciprofloxacin; 258 musculoskeletal events occurred in 232 paediatric patients (some patients had more than one musculoskeletal AE). This gave an estimated risk of 16 musculoskeletal AEs per 1000 patients receiving ciprofloxacin (1.6%, 95% CI 0.9% to 2.6%) or one musculoskeletal AE in every 62.5 patients. A summary of the reported symptoms and/or signs of arthropathy is presented in table 4. Only 10 of the 32 studies gave detailed information regarding time and onset, duration of follow-up, method of detecting arthropathy and management.

The youngest documented case of arthropathy was in a 7-month-old infant.[60] Age of occurrence was documented in 47 paediatric patients; median age was 10 years. The time to follow-up of the patients after use of ciprofloxacin was 1 week to 50 months.[80 109] Of 47 studies reporting the time to follow-up of the patients, 31 studies (66%) followed up for an average time of ≥90 days. The time to development of any form of arthropathy was reported in 12 studies and ranged from 15 min to 30 days (median 6 days).[73 81] There were three additional cases of arthralgia that occurred on the first day of treatment.[16 101] Management included continuation of drug use, discontinuation of drug with/without rechallenge, use of analgesics to relieve arthralgia, dose reduction or a combination of any of these measures. All cases of arthropathy with report on management resolved or improved. However, there was a report of arthralgia remaining unchanged in 1 out of 31 reported arthralgia cases in a study. However, we are not certain if any management was instituted or for how long the arthralgia persisted.[74]

Arthralgia accounted for 130 (50%) events. Four patients discontinued therapy due to arthralgia, which resolved in three patients (no report of the outcome in the last patient).[47 68] Radiological confirmation of arthropathy using MR1 was positive in two studies involving six cystic fibrosis patients, who had joint effusions, abnormal thickness of articular cartilage, non-homogeneous structure of cartilage or altered two-layer appearance of cartilage.[79 91] In addition to clinical examination and radiological investigation, seven studies (531 cases and 674 controls) investigated the effects of ciprofloxacin on growth of patients after following up the patients for 6–50 months.[28 32 33 63 75 109 116] None of these studies found

Table 3 Summary of serious adverse events necessitating withdrawal and/or discontinuation of therapy

AE	Number of patients (n=23)
Rash	5
Arthralgia	4
Vomiting and diarrhoea	2
Allergy	2
Anaphylactoid reaction	2
Epistaxis	1
Angioneurotic oedema	1
Cardiac failure	1
Sinus nodal arrest	1
Toxic megacolon	1
Nausea	1
Interstitial nephritis	1
Benign intracranial hypertension	1

Table 4 Summary of reported musculoskeletal events from 32 studies

Musculoskeletal events	Frequency (%)
Arthralgia	130 (50.0)
Tendon or joint disorder	48 (19.0)
Reduced movement/stiffness	39 (15.0)
Joint swelling	8 (3.0)
Radiological confirmed arthropathy	6 (2.3)
Myalgia	4 (1.6)
Arthritis	3 (1.2)
Pain in extremity	1 (0.4)
Osteitis	1 (0.4)
Unknown	18 (7.0)
Total	258* (100)

*258 musculoskeletal events occurred in 232 patients.

any significant difference in growth of the ciprofloxacin exposed patients compared with the control arm.

The majority of the musculoskeletal events (223, 86%) were classified as possibly related to ciprofloxacin. Rechallenge with ciprofloxacin was done in eight patients, but was positive in only a 9-year-old cystic fibrosis patient who had received 17 mg/kg/day for 15 days and noticed arthralgia of elbow and knees on the sixth day post-therapy.[83 91 101] No information was given about how long arthralgia lasted on rechallenge and if any management was instituted.

Controlled studies

Only two studies estimated the risk of development of arthropathy in paediatric patients receiving ciprofloxacin compared to a control group. A prospective cohort study of 264 cases and 249 controls matched for age and presence of cystic fibrosis, followed up patients for 15 days after the last dose of treatment.[101] An estimated crude OR for musculoskeletal AEs in the fluoroquinolone group (ciprofloxacin, ofloxacin and perfloxacin) compared to other antibiotics was 9.3 (95% CI 1.2 to 195, p=0.02). Considering cystic fibrosis patients alone within the same study (approximately 90 patients in each group), the OR for musculoskeletal AEs in the fluoroquinolone group compared to other antibiotics was 1.2 (95% CI 0.1 to 35, p=0.99). The ORs estimated were not adjusted for possible influence of age and sex.

Second, a retrospective cohort study using a pharmacy database of patients exposed to fluoroquinolones and azithromycin, checked for potential joint or tendon disorder diagnosed within 60 days of exposure to drug.[103] The joint or tendon disorders were verified from medical records of the patients by three blinded specialists. The study had over 4500 patients receiving ciprofloxacin and over 1500 patients receiving ofloxacin compared to over 15 000 patients receiving azithromycin. The estimated RR for verified tendon or joint disorder for ciprofloxacin was 1.04 (95% CI 0.72 to 1.51) and for ofloxacin was 1.04 (95% CI 0.55 to 1.84). The age and sex adjusted RR were 1.08 (95% CI 0.74 to 1.58) for ciprofloxacin and 1.13 (95% CI 0.63 to 2.03) for ofloxacin.

Safety data of all randomised controlled trials, non-randomised controlled trials and cohort studies in our review were pooled together. Analysis of 23 controlled studies (7 controlled studies were excluded because ciprofloxacin or another fluoroquinolone was administered in the comparator arm) comprising 6481 cases and 17 441 controls showed that there is a 57% increased risk of arthropathy in patients who received ciprofloxacin compared to the comparator arm (OR 1.57, 95% CI 1.26 to 1.97).[13 15–19 28–33 63 75 76 79 101 103 105 109 111 112 116] Further analysis of five controlled studies that included only cystic fibrosis patients (227 cases and 391 controls) estimated a 67% increased risk of arthropathy (OR 1.67, 95% CI 1.13 to 2.45).[17 19 79 101 105]

DISCUSSION

Our systematic review about the safety of ciprofloxacin is the first review that has pooled together all reported suspected AEs due to ciprofloxacin use in paediatric patients. Ciprofloxacin is contraindicated in paediatrics because juvenile animals developed arthropathy after use.[4] However, our review has identified over 16 000 children who have received ciprofloxacin. It is likely that the number of children who have received ciprofloxacin in practice is significantly greater than this.

Our review confirms that musculoskeletal toxicity is the most frequently reported AE following the use of ciprofloxacin. There is, however, a wide range of toxicity that has been reported and it is important to recognise that, like all anti-infective agents, ciprofloxacin can be associated with a broad spectrum of AEs. The toxicity profile in table 2 is pooled safety data of reported suspected AEs by individual authors; however, these AEs may not be adverse drug reactions in all cases. From our review, there is an estimated risk of one musculoskeletal AE in every 62.5 patients, and a 57% increased risk of arthropathy in patients exposed to ciprofloxacin. The musculoskeletal AEs appear reversible with management.

The term arthropathy has been used broadly for various musculoskeletal AEs. Juvenile animals were noted to have gait stiffness, particularly in the hind limbs; reluctance to rise from a sitting, lateral or sternal recumbence position; exudation of synovial fluid; and blistering and ulcerative erosions of articular cartilage in the limb joints.[4 118] However, our review suggested that arthralgia was the commonest symptom of arthropathy (50%) in paediatric patients, affecting mostly the knee joint. Tendon or joint disorders and reduced movement also accounted for a significant proportion of arthropathy cases (19% and 15%, respectively). Although the specific tendon disorder could not be ascertained, tendinitis or tendon rupture could be implied as this represents the most frequent presentations in the literature.[119–121] The only specific report of tendon disorder in our review was a case of Achilles tendinitis in a patient (age not specified).[106] Tendon disorders have been

thought to occur more frequently in patients over 60 years.[122] However, our review suggests it is also reported in paediatric patients, and clinicians should be aware of such possibility.

Various molecular mechanisms have been postulated for arthropathy, such as inhibition of synthesis of collagen and glycosaminoglycans, inhibition in mitochondrial function resulting in generation of free radicals and oxidative stress or chelation of magnesium ions, all culminating in cartilage and tendon damage.[5 123]

There appear to be differences in features of arthropathy in animals compared to humans. Two studies reported on the histopathology of the articular cartilage of three patients at postmortem examination, but no arthropathic lesions were noted.[64 91] However, animal studies showed exudation of synovial fluid, blistering and ulcerative erosion of articular cartilage at postmortem examination, even after clinical recovery.[4]

Animal studies have suggested that arthropathy occurs earlier in younger animals.[118] However, our review showed a median age of 10 years (range 7 months to 17 years) among 47 age documented paediatric patients. Although most of the studies included in our review involved children (2–11 years), at least 389 neonates were exposed, with none developing musculoskeletal AEs. The differences in growth between animals and humans have been suggested as a possible explanation for such differences. The number, location and time of appearance of secondary ossification centres vary between animal species and humans.

Arthropathy in animals appears to be dose related, with increased risk in higher doses and after longer duration of treatment.[124 125] However, our data does not point to any dose dependent or duration dependent relationship in humans.

In conclusion, our review identified only one prospective cohort study showing an increased risk of arthropathy, and we estimated an increased risk in those exposed to ciprofloxacin. The concern of arthropathy in paediatric patients, based on studies in juvenile animals is therefore appropriate; however, the risk of arthropathy is relatively low and reversible with management. The risk of ciprofloxacin-induced arthropathy needs to be considered in relation to the benefits of using ciprofloxacin in children with acute infections. The role of ciprofloxacin in paediatric and neonatal sepsis can only be clarified by further prospective studies evaluating both the benefit and the risk of toxicity, with a particular focus on the risk of arthropathy.

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