What is the evidence of safety of quinolone use in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the evidence for the safety of quinolone use in children?*

Quinolones are widely advocated throughout the WHO Pocketbook of Hospital Care for Children in the treatment of serious bacterial infection.

The WHO Pocketbook of Hospital Care for Children makes recommendations about 2 quinolone antibiotics;

1. Ciprofloxacin: Oral 10-15mg/kg per dose given twice per day for five days (maximum 500mg/dose). Use in children is only warranted if the benefits outweigh the risk of arthropathy. (Pocketbook Appendix 2, pg. 333).

2. Nalidixic acid: oral 15mg/kg 4 times a day for five days (Pocketbook Appendix 2, pg. 341)

Ciprofloxacin is recommended as a suitable first line agent for the treatment of dysentery. The PocketBook notes that most episodes of dysentery are due to Shigella and nearly all require antibiotic treatment. Non quinolone antibiotics; metronidazole, streptomycin, tetracyclines, chloramphenicol, sulfonamides, nitrofurans, aminoglycosides, first and second generation cephalosporins and amoxicillin are not effective. Pivmecillinam is an appropriate second line agent. (Pocketbook pg. 128). The pocketbook further recommends the possible use of ciprofloxacin for typhoid fever, but not as first line therapy. (PocketBook Pg. 160).

Nalidixic acid, a first generation quinolone has been used for decades in the paediatric population. Although, like other quinolones it too can cause cartilage toxicity in juvenile animals, it has been established to not have this effect in humans and is used routinely in children. , This review does not address the use of nalidixic acid, but focuses on newer fluoroquinolones, with particular emphasis on ciprofloxacin.

INTRODUCTION

Fluoroquinolones act through the inhibition of bacterial DNA gyrase and have broad spectrum activity against gram-positive, gram-negative and some atypical bacteria. They are particularly effective against Staphylococci, Shigella and Pseudomonas. Oral bioavailability is excellent and, high tissue and body fluid concentrations are achieved. Fluoroquinolones have been used in the management of systemic infections, lower and upper respiratory infections, urinary tract infections, gonococcal urethritis, skin, bone and gastrointestinal infection. [4]

Historically, there was concern about the use of fluoroquinolones in children, because of the cartilage toxicity and arthropathy found in animal studies; this was species and dose specific.[5] The major paediatric patient groups to whom fluoroquinolones have been administered include those with Cystic Fibrosis, complex genitourinary disorders, salmonella infection, severe bacterial infection not responding to initial therapy and immunocompromised children (chemotherapy, transplantation and inherent immunodeficiency). [5]

The use of fluoroquinolones has increased over the last decade, providing a large population on whom the effects of this drug can be monitored. In fact, in The United States 14,000 courses are prescribed for children under 10 and 28,000 courses for children between 10 and 14 each year.[5]

In addition to the specific uses detailed above, the role of the fluoroquinolones is further expanding for two major reasons. Firtsly, the development of antimicrobial resistance in many common infective microorganisms has made flurorquinolones the most rational agent of choice. Secondly, in developing countries, the ease of administration of an oral therapy, for conditions that may otherwise require IV antibiotics, is an attractive option. [6]

METHODOLOGY

The PubMed Clinical Queries search strategy was employed: Category; therapy. Scope; broad and sensitive. The clinical search strategy employed was: ((quinolone$) OR (ciprofloxacin) AND (safety)). The limits "Newborn: birth – 1 month, Infant 1-23 months, Preschool Child: 2-5 years, Child: 6 – 12 years, English and Humans were applied. 56 articles were found.
The Cochrane database was also searched with the MeSH terms quinolones, ciprofloxacin and drug toxicity, and was limited to reviews. This yielded no additional articles.
All abstracts were read and relevant articles sourced. Studies were excluded if they did not address systemic fluoroquinolone use, were not clear about the proportion of paediatric subjects or did not consider safety as a major focus of the article. Review papers more than 15 years old were excluded, unless considered to be seminal.

There were 7 Randomised Controlled Trials (RCTs), 9 review articles, 11 cohort studies, 2 case-control studies and 1case report.
26 articles were excluded. 12 articles discussed topical use of fluoroquinolones only. 3 articles were not specific to the paediatric population. 4 articles did not deal adequately with fluoroquinolone safety. The remaining 7 articles were irrelevant.

RESULTS

Of the 7 RCTs 6 studies compared fluoroquinolone antibiotics against other antimicrobial agents for efficacy and safety [7-12] and 1 study compared ciprofloxacin dosing schedules. [13]

The studies that compared fluoroquinolones with other antimicrobial agents all concluded that they were equally efficacious and had similar safety profiles to the alternative agents.[7-12]

Two studies were of particular importance to the use of ciprofloxacin in dysentery. The first evaluated efficacy and safety of oral ciprofloxacin compared with IM ceftriaxone in 201 children between 6 months and 10 years of age (70% < 3 years). Possible drug related adverse events occurred in 8% of the ciprofloxacin and 4.7% of the ceftriaxone group. [5] children were considered to have serious adverse events, and these were all in the ciprofloxacin group. However, the serious adverse events included 1 child who had a generalised seizure 20 minutes after enrolment and 4 children who had vomiting and diarrhoea severe enough to warrant IV rehydration. All other events were mild and transient. Joint examination was normal, during and 3 weeks post treatment, in all patients. Importantly, in the Ciprofloxacin group drug serum levels were measured, and more than 95% had adequate serum levels to treat Shigella and Salmonella and, the clinical outcomes were the same in both groups.[7] The second study compared oral ciprofloxacin and pivmecillinam in 143 children between 2 and 15 years with dysentery. Again, the two treatments were equally efficacious. There were high rates of arthralgia noted in both groups (ciprofloxacin; 18% vs. pivmecillinam; 22%). However, there was no arthritis noted in either group and, all arthralgia resolved.[8]

Three of the RCTs examined the use of ciprofloxacin in managing pulmonary exacerbations in cystic fibrosis.[9], [10], [11] All of these studies found ciprofloxacin to be equally efficacious compared to other standard regimes. There was no increased arthropathy in the ciprofloxacin groups above that expected in this cohort.[22] In reporter blinded assessments, including physical examination, ultrasound and MRI Richard et al found no evidence, in 108 children, of increased rates of arthralgia, arthropathy or cartilage damage.[9] Scaahd et al found no impact on overall growth over a period of three months in a group of 44 patients between 8 and 25 years.[10]

One RCT compared ciprofloxacin with rifampicin for safety and efficacy in the eradication of nasopharyngeal carriage of Neisseria meningitides. Ciprofloxacin had similar rates of eradication to rifampicin and there was no significant difference in side effects. In the 1875 patients, 469 of whom were under 18 years there were no children who developed any joint problems.[12]

The RCT comparing various ciprofloxacin regimines, studied 253 children between 12 months and 12 years with Shigella dystenteriae and found that both standard and short course ciprofloxacin resulted in bacteriological cure. There was no difference in the drug related side effects between groups. 4 patients in each group reported mild arthralgia during treatment which resolved, and all patients had normal joint function at follow up 2 weeks later.[13]

There were 9 review articles that met the criteria for this paper. 5 concluded that the use of fluoroquinolones, particularly ciprofloxacin, is efficacious and safe in children, but that ongoing caution is required. [5], [14], [15], [16], [17] 3 reviews, 2 of which were more than 15 years old, concluded that the fluoroquinolones appeared to be well tolerated but required further investigation.[18], [19], [20]

One review discussed the need for a sensible approach to the use of quinolones in developing countries, given issues of resistance, and the need for simple and effective therapy for a range of conditions that cause a heavy burden of disease.[21]

Many of the reviews cite papers reporting results from large international and national databases, in addition to collating evidence from RCTs, cohort and case-control studies. However, nearly all of the reviews fail to provide clear information about how the literature searches for the review were conducted or, the criteria that authors used to include and exclude studies. Although this must be acknowledged as a limitation it is important to recognise that there are inherent difficulties in accurately describing the adverse events (AE) profile of any drug. However, the review papers, despite their limitations, still contain important information on the pattern of AE associated with fluoroquinolone use in large numbers of paediatric patients, over long periods of time, from a variety of countries.

The reviews indicate an overall adverse events rate in children between 13 – 20%, which is comparable to many other antimicrobial agents. The range is affected by the duration of treatment and the particular fluoroquinolone used. [5], [14] [15], [16], [17]

Most side effects were found to be mild and transient. The most commonly reported problems were gastrointestinal (diarrhoea and nausea) and central nervous system disturbance (headache and dizziness). These occurred at frequencies of between 2-20%, again depending on the duration of use and the fluoroquinolone.

The reviews that commented specifically on joint involvement found rates of arthralgia between 1-5% and rates of arthropathy less than <1%. [5],[15], [16], [17]

It was noted that both arthralgia and arthropathy nearly always resolved with cessation of treatment. The first exception to these generally low rates were the cohorts with cystic fibrosis, where the baseline rate of arthralgia is 4% in childhood through to 7-8% in adolescence.[22] In the fluoroquinolone studies this group has been shown to have arthralgia rates consistent with the expected baseline. Secondly, one review paper cites a study by Salam et al with unusually high rates of arthralgia, at 18%. This study is discussed above in the section on RCTs.[8]

Rare, but serious side effects that have been recorded include cardiovascular (QT prolongation), musculoskeletal (tendonitis and tendon rupture), endocrine (glucose homeostasis dysregulation), renal problems and seizures. These more serious side effects have been associated with select populations, such as those with predisposing conditions, like heart disease, renal failure or diabetes, or the elderly, and, with certain quinolones like gatifloxacin and levofloxacin. [15]

There were 8 cohort studies. All studies had efficacy results and AE profiles consistent with results in the RCTs discussed above. 4 studies were based on information from databases for reporting AE, or databases specifically designed to document "compassionate use" in children, which was the historical term to describe the use of fluroquinolones where the benefits were felt to outweigh potential costs. [23-26] The remaining 4 studies analysed clinical cohorts of children receiving ciprofloxacin for cystic fibrosis management [27], [28] or mixed medical indications.[29], [30]

The studies that drew information from databases used a range of international sources, with varying patient numbers. The Hampel cohort, had the largest sample size (n=1795, with 2030 treatments occurring), patients received an average of 8mg/kg/day of IV ciprofloxacin or 25mg/kg/day of oral ciprofloxacin. The overall AE rate was 10.9% for oral therapy and 18.9% for IV therapy. The rate of arthralgia was 1.5%. [23]

The cohort studies on cystic fibrosis patients demonstrated adequate efficacy, and the AE were also consistent with other studies for ciprofloxacin. Redmond et al demonstrated no signs or symptoms of arthropathy, or arthropathic changes on MRI three months post 2 weeks of ciprofloxacin treatment in 26 children aged 6-16.[28] Pradhan et al also demonstrated an absence of arthropathic change on MRI in 58 children, given 9-16 days of oral ciprofloxacin.[30]

There were 2 Case-Control studies, both undertaken in neonates who had received IV ciprofloxacin. The first group, studied 48 preterm neonates, treated for a mean of 11 days. Over a follow-up period of 2 years they found no osteoarticular problems, joint deformities or, differences in growth and development.[31] The second group studied 30 term neonates, treated for 14 days and found no difference in either acute biochemical and haematological markers, or serial ultrasounds which demonstrated no difference in knee or tibial cartilage at 1 and 6 months between the study and control group. [32]

There was one case report of ciprofloxacin associated psuedomembranous colitis. This was in a child with multiple, severe, medical problems. The authors acknowledged that there were no other reports in the literature of such an occurrence.[33]

DISCUSSION

The role of the fluoroquinolones, particularly ciprofloxacin, in the management of a variety of childhood infections has been controversial. The benefits, including ease of administration and efficacy in treating infections, where multidrug resistance is a problem, demands resolution of the issue of safety.

A significant body of evidence has now been amassed from the ongoing administration of compassionate-use fluroquinolones, in addition to an increasing number of clinical studies that have been undertaken, addressing issues of efficacy and safety.

The efficacy of the fluoroquinolones has been shown to be at least equal, if not better, than other standard antimicrobial agents in treating a range of infections. Ciprofloxacin particularly is an excellent agent for the management of dysentery and a good agent for typhoid fever.

The evidence shows that the AE rate for most fluoroquinolones is comparable to other antimicorbial agents, and that most AE are mild and transient. This AE profile is made even more acceptable when considered in light of the severity of the conditions being treated. Furthermore, within its class ciprofloxacin has been shown to have one of the most benign profiles of the fluorquinolones.

When considering joint toxicity there is no evidence that permanent arthritis is induced by quinolone use in humans. The development of transient arthritis is rare and and no studies utilising radiographic techniques, or monitoring growth and joints over long time periods have noted any adverse outcomes. The development of arthralgia may be slightly higher with the fluorquinolones than other antimicorbials, but is mild and transient. Furthermore, recent studies that address the use of fluoroquinolones in neonates, where one would expect the cartilage and joints to be most vulnerable, have shown no evidence of joint toxicity developing in these children over monitoring periods of several years.

SUMMARY

Fluroquinolones are efficacious antimicrobial agents with an important role in the treatment of a variety of paediatric infections. Ciprofloxacin is a particulary useful fluorquinolone for dysentery and typhoid.

There is grade A evidence to support both the overall safety of ciprofloxacin use in children and lack of joint toxicity.

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