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Review Article

Clinical pharmacology of ciprofloxacin in paediatric patients

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Abstract

Ciprofloxacin is a fluoroquinolone and targets bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria topoisomerase IV is the primary target. In contrast, DNA gyrase is the primary quinolone target in many gram-negative microbes. Ciprofloxacin inhibits gyrase-mediated DNA supercoiling at concentrations that correlate with those required to inhibit bacterial growth. Ciprofloxacin is active against Proteus, Escherichia coli, Klebsiella, Chlamydia, Mycoplasma, Legionella, Brucella and Salmonella, Shigella, Enterobacter, Campylobacter, Mycobacterium species. Ciprofloxacin is rapidly absorbed following oral dosing and the total body clearance and the distribution volume increase with the infant maturation and child development whereas the elimination half-life decreases with subject ageing and ranges from 16.6 to 3.3 hours in infants and adolescents, respectively. Ciprofloxacin has been found efficacy and safe in infants and children but it can causes adverse-effect, the major adverse-effect is musculoskeletal abnormalities but they are reversible. Several interactions of ciprofloxacin with drugs have been reported. Prophylaxis with ciprofloxacin is useful to prevent infections and treatment with ciprofloxacin has been used to treat different infections in infants and children. Ciprofloxacin poorly crosses the human placenta and poorly penetrates into the beast-milk whereas it penetrates into the cerebrospinal fluid in significant amounts and successfully cured bacterial meningitis in infants and children. The aim of this study is to review the published data on ciprofloxacin dosing, efficacy and safety, adverse-effects, pharmacokinetics, intersection with drugs, prophylaxis, treatment, placental transfer, penetration into the breast-milk and cerebrospinal fluid, and treatment of meningitis in infants and children.

INTRODUCTION

Ciprofloxacin

The introduction of ciprofloxacin in the clinical use represents a particularly important therapeutic advance. Ciprofloxacin has a broad antimicrobial activity and is effective after oral administration for the treatment of a wide variety of infectious diseases [1].

Mechanism of action of ciprofloxacin

Ciprofloxacin targets bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria, topoisomerase IV is the primary target. In contrast, DNA gyrase is the primary quinolone target in many gram-negative microbes. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling that can occur during DNA replication. Ciprofloxacin inhibits gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth. Mutation of the gene that encodes the A subunit of the gyrase can confer resistance to ciprofloxacin. Topoisomerase IV, which separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication, also is a target for ciprofloxacin. Eukaryotic cells do not contain DNA gyrase. They do contain a conceptually and mechanistically similar type II DNA topoisomerase, but ciprofloxacin inhibits it only at concentrations (100 to 1,000 µg/ml) much higher than those needed to inhibit the bacterial enzyme [1].

Antimicrobial activity of ciprofloxacin

Ciprofloxacin is a potent bactericidal agent against Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter and Campylobacter. While once a standard therapy for Neisseria gonorrhoeae infections, resistance has increased to the point these agents are no longer recommended in many countries for empiric therapy of gonorrhoea. Some fluoroquinolones, thus ciprofloxacin, are active against Pseudomonas species having substantial enough activity for use in systemic infections. Fluoroquinolones have good in-vitro activity against staphylococci, but they are less active against methicillin-resistant strains, and there is concern over development of resistance during therapy. Activity against streptococci is significantly greater with the never fluoroquinolone agents, including ciprofloxacin. Several intracellular bacteria are inhibited by ciprofloxacin at concentrations that can be achieved in plasma; these include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium tuberculosis. Ciprofloxacin has

MIC value from 0.5 to 3 μg/ml for Mycobacterium fortuitum, Mycobacterium kansasii, and Mycobacterium moxifloxacin also has useful activity against anaerobes [1].

Absorption, distribution, metabolism and excretion of ciprofloxacin

Most quinolones, thus ciprofloxacin, are well absorbed after oral administration. Peak serum concentrations of fluoroquinolones are obtained with 1 to 3 hours after oral dose. The distribution volume of quinolones is high, with concentration in urine, kidney, lung, and prostate tissue and stool, bile, macrophages and neutrophils higher than in serum levels. Ciprofloxacin has been detected in breast-milk because of its excellent bioavailability; the potential exists for substantial exposure of nursing infant. Ciprofloxacin is cleared predominantly by the kidney, and dosages must be adjusted in renal failure.

Literature search

The literature search was performed electronically using PubMed database as search engine. The following key words were used: "ciprofloxacin dosing infants, children", "ciprofloxacin efficacy, safety infants, children", "ciprofloxacin adverse-effects infants, children", "ciprofloxacin pharmacokinetics infants, children", "ciprofloxacin drug interactions", "ciprofloxacin prophylaxis children", "ciprofloxacin treatment infants, children", "ciprofloxacin placental transfer", "ciprofloxacin breast-milk", and "ciprofloxacin meningitis infants, children". In addition, the books: The Pharmacological Basis of Therapeutics [1] and the Births National Formulary for Children [2] were consulted.

RESULTS

Administration schedules of ciprofloxacin to infants and children

Oral treatment of infants for severe respiratory-tract infections and gastrointestinal infection

Infants. Give: 15 mg/kg twice-daily.

Intravenous admiration to infants for severe respiratory-tract infections and gastrointestinal infection

Infants. Give: 10 mg/kg twice-daily, to be given over 60 min of infusion.

Oral treatment of complicated urinary-tract infections

Infants. Give: 10 mg/kg twice-daily.

Intravenous treatment of complicated urinary-tract infections

Infants. Give: 6 mg/kg twice-daily to be given over 60 min of infusion.

Oral prevention of secondary case of meningococcal meningitis

Infants. Give: 30 mg/kg (maximum per dose = 125 mg) for 1 dose.

Oral or intravenous administration to children:

Oral treatment for Fistulating Crohn's disease

Children. Give: 5 mg/kg twice-daily.

Intravenous treatment of children for severe respiratory-tract infections and gastrointestinal infections

Children. Give: 10 mg/kg thrice-daily (maximum per dose = 750 mg).

Oral treatment of acute exacerbation of bronchiectasis

Children aged 1 to 17 years. Give: 20 mg/kg twice-daily (maximum per dose = 750 mg).

Intravenous treatment of acute exacerbation of bronchiectasis

Children aged 1 to 17 years. Give: 10 mg/kg thrice-daily (maximum per dose = 400 mg) to be given over 60 min of infusion.

Intravenous treatment for complicated urinary-tract infections

Children. Give: 10 mg/kg twice-daily, the dose should be doubled in severe infection (maximum per dose = 750 mg twice-daily).

Children. Give: 6 mg/kg thrice-daily, increase the dose to 10 mg/kg thrice-daily in severe infection (maximum per dose = 400 mg twice-daily).

Oral treatment of gonorrhoea

Children aged 12 to 17 years. Give: 500 mg for 1 dose.

Oral treatment of anthrax (treatment and post-exposure prophylaxis)

Children. Give: 15 mg/kg twice-daily (maximum per dose = 500 mg)

Intravenous treatment of anthrax (treatment and post-exposure prophylaxis)

Children. Give: 10 mg/kg twice-daily (maximum per dose = 400 mg)

Oral prevention of secondary case of meningococcal meningitis

Children aged 1 month to 4 years. Give: 30 mg/kg (maximum per dose = 125 mg) for 1 dose.

Children aged 5 to 11 years. Give: 250 mg for 1 dose.

Children aged 5 to 11 years. Give: 500 mg for 1 dose.

Efficacy and safety of ciprofloxacin in infants and children

Ciprofloxacin was found efficacy and safe in neonates with sepsis [3]. Ciprofloxacin is potentially a safe alternative to be used in children aged < 18 years when there is no better alternative [4]. Ciprofloxacin therapy in the treatment of immunosuppressed paediatric burn patients is safe and efficacious and at therapeutic doses does not cause arthropathy [5]. Ciprofloxacin may be recommended for use in children for short duration when

effective alternative antibacterials are unavailable [6]. The safety profile of ciprofloxacin in children and adolescents is very similar to that observed in adult patients. Adverse events were noted in only 5 to 15% children, with gastrointestinal, skin and central nervous system reactions being the most common. Reversible arthralgia occurred in 36 out of 1,113 children (3.2%) with cystic fibrosis, and in no case could cartilage damage be demonstrated by radiographic procedures. Thus, these data clearly suggest that the administration of ciprofloxacin to children is effective and safe [7]. Of 630 paediatric patients, aged 3 days to 17 years, received ciprofloxacin at a median dose 25.2 mg/kg and the median duration of therapy was 22.8 days. Arthralgia considered by the treating physicians to be related to ciprofloxacin was reported in only 8 children (1.3%), all of whom were females, and arthralgia resolved in all children. Some of these children were given subsequent courses of ciprofloxacin with no complaints of arthralgia. Overall, the safety profile of ciprofloxacin in children is not substantially different from that of adults [8].

Adverse-effects caused by ciprofloxacin in infants and children

In 184 paediatric patients, aged ≤ 17 years, treated with ciprofloxacin there were 1,065 adverse-effects. The most frequent adverse-effects were: musculoskeletal, abnormal function test, nausea, change in white blood cell count, and vomiting. The musculoskeletal adverse-effects were reversible with management. Further studies should be carried out with particular focus on the risk of arthropathy [9]. The highest rate of reported gonorrhoea infections occur among adolescent females aged 15-19 years. A single dose of 500 mg ciprofloxacin was administered to children aged 15 to 19 years. Children appear to outweigh the benefits. Reports of irreversible cartilage toxicity or age-associated adverse-effects were observed in 5,236 infants, children and adolescents (aged 5 days to 24 years) treated with a total of 5,486 courses of fluoroquinolones [10]. Choonara [11] reviewed the adverse-effects caused by ciprofloxacin in children aged ≤ 17 years. In 105 articles involving 16,184 paediatric patients 1,065 adverse-effects were reported (risk 7%, 95% confidence interval = 3.2 to 14.0%) and the most adverse-effects were: musculoskeletal, abnormal liver function test, nausea, change in white cell count, and vomiting. Ciprofloxacin related death occurred in a newborn infant. The musculoskeletal adverse-effects were 258 which occurred in 232 paediatric patients. Arthralgia accounted for 50% of these. The age of occurrence of arthropathy ranged from 7 months to 17 years (median, 10 years) and all cases or arthropathy resolved or improved with management.

Pharmacokinetics of ciprofloxacin in infants

Zhao et al. [12] studied the pharmacokinetics of ciprofloxacin in 60 infants with a median postmenstrual age of 36.5 weeks (range, 24.9 to 47.9), postnatal age of 27.0 days (range, 5.0 to 121), and body-weight of 1,115 grams (range, 540 to 3,850). Ciprofloxacin was administered intravenously at a dose of 7.5 mg/kg twice-daily to infants with a postmenstrual age ≥ 34 weeks (84%) and at a dose of 12.5 mg/kg in infants with longer postmenstrual age. The median dose was 9.7 mg/kg (range, 9.7 to 11.0) and the median duration of treatment was 5 days (range, 1 to 17). Infants were infected by Enterobacter species resistant to standard treatment and when there was a risk of meningitis. Table 1 summarizes the pharmacokinetic parameters of ciprofloxacin.

Central DV = central distribution volume. Peripheral DV = peripheral distribution volume. Q = intercompartmental clearance. TBC = total body clearance. F inotrope = scaling factor applied for infants co-administered with inotropic agents.

This table shows that the central distribution volume is greater than the water volume and is similar to the peripheral volume indicating that ciprofloxacin is distributed into the whole body and there is a remarkable interindividual variability in the pharmacokinetic parameters.

Pharmacokinetics of ciprofloxacin in infants and young children

Peltola et al. [13] assessed the pharmacokinetics of ciprofloxacin 7 infants, aged 5 to 14 weeks, and in 9 children aged 1 to 5 years. A single oral dose of 15 mg of ciprofloxacin was administered to all subjects who were infected by Salmonella. (Table 2) summarized the pharmacokinetic parameters of ciprofloxacin.

Table 2. Pharmacokinetic parameters of ciprofloxacin which are obtained in 7 infants and 9 children. Figures are the mean+SD, by Peltola et al. [13].

*Student t test for unimpaired data.

This table shows that the absorption half-life and the time to reach the peak concentration are similar in infants and in children. In contrast, the elimination half-life, AUC, and the mean residence time are lower in children suggesting that ciprofloxacin is more rapidly eliminated in children than in infants because renal function is greater in children.

Pharmacokinetics of ciprofloxacin in infants, children, and adolescents

Payen et al. [14] investigated the pharmacokinetics of ciprofloxacin in 3 newborn infants, aged 1.4 days (range, 1.1 to 2.2) and weighing 2.1 kg (range, 1.7 to 3.5), in 17 infants aged 0.5 years (range, 28 days to 23 months) and weighing 5.5 kg (range, 0.75 to 9.2), in 27 children, aged 5.6 years (range, 2 to 11) and weighing 18.6 kg (range 8 to 130), and in 8 adolescents, aged 16.4 years (range, 12 to 24) and weighing 42.3 kg (range, 28 to 58). Thirteen of children and 7 adolescents were suffering from cystic fibrosis. Fifteen children had dysuria or polyuria and the strains isolated were: Pseudomonas aeruginosa, group D streptococci, Enterobacter cloacae, Escherichia coli, Klebsiella species, Pseudomonas pickettii, and Enterococcus faecalis. The fever was caused by Klebsiella species, Pseudomonas cepacia, Serratia, and Escherichia coli. Ciprofloxacin was intravenously infused at a dose of 10 mg/kg followed by oral ciprofloxacin at a dose of 15 mg/kg twice-daily to the subjects with cystic fibrosis, a second group of subjects, aged 2 days to 8 years, received 5 to 17 mg/kg of ciprofloxacin intravenously twice-daily, a third group of subjects, aged 1 to 13 years, received ciprofloxacin intravenously at a dose 7.5 to 30 mg/kg twice-daily, and the fourth group of subjects, aged 1 day to 4 years, received ciprofloxacin intravenously at a dose of

Table 1:

	Full data set		Bootstrap	
Parameter	**Final estimate**	**%Relative error**	**Median**	**5th – 95th Percentile**
Central DV (L)	1.97	17.7	1.82	0.78 – 2.59
Peripheral DV (L)	1.93	21.9	1.97	1.38 – 3.02
Q (L/h)	2.5	32.6	2.62	1.02 – 5.41
F inotrope	0.366	6.0	0.365	0.323 – 0.407
Renal function	-0.00335	46.0	-0.00331	-0.00753 to -0.00063
F inotrope	0.708	10.9	0.719	0.572 – 0.869
Interindividual variability (%)				
Central DV	48.1	63.6	49.6	26.2 – 77.2
Peripheral DV	49.3	68.3	51.2	15.8 – 76.9
TBC	33.2	19.9	31.3	25.7 – 37.4
Interoccasion variability (%)				
TBC	16.4	55.6	16.6	9.2 – 26.9
Residual variability	19.3	28.2	18.7	14.8 – 23.1

Table 2:

Subjects	Peak conc. (µg/ml)	Time to peak conc. (h)	Absorption half-life (h)	Elimination half-life (h)	AUC0-∞ (µg*h/ml)	Mean residence time (h)
Infants	3.3±1.3	1.18±0.46	0.40±0.22	2.73±0.28	16.6±7.4	4.6±0.8
Children	2.1±1.7	1.00±0.25	0.29±0.16	1.28±0.52	5.3±3.3	2.4±0.6
*P-value	>0.05	>0.05	>0.05	< 0.001	< 0.01	0.001

Table 3:

Group (age) and parameter	Total body clearance (L/h)	Elimination half-life (h)	Distribution volume (L)
Newborn infants aged 1.1 to 2.2 days (N = 3)			
Minimum	0.11	10.5	3.8
Maximum	0.82	24.5	1.2
Mean	0.39	16.6	7.9
%Coefficient of variation	96.0	42.9	63.4
Older infants aged 28 days to 23 months (N = 17)			
Minimum	0.29	3.2	2.4
Maximum	8.79	12.8	41.1
Mean	2.93	6.2	20.9
%Coefficient of variation	87.5	37.9	55.3
Children aged 2 to 11 years (N = 27)			
Minimum	0.58	1.8	16.6
Maximum	37.4	19.9	141
Mean	17.7	4.2	73.4
%Coefficient of variation	59.6	64.3	43.6
Adolescents aged 12 to 24 years (N = 8)			
Minimum	21.7	2.4	103
Maximum	50.3	4.9	244
Mean	35.7	3.3	166
%Coefficient of variation	22.9	18.5	28.5

8 to 15 mg/kg twice-daily. Table 3 shows the pharmacokinetic of ciprofloxacin obtained in these subjects.

Table 3. Pharmacokinetic parameters of ciprofloxacin which are obtained in 3 newborn infants, 17 older infants, 27 children, and 8 adolescents, by Payen et al. [14].

This table shows that the total body clearance and the distribution volume increase with the subject age. In contrast, the elimination half-life decreases with the subject age. These results may be explained by increasing renal function and hepatic metabolism which increase with the subject aging. The %coefficient of variation is greater in the newborn infants, older infants and in children that in adolescents. This remarkable variability may depend by the wide range of age in infants and children.

Interaction of ciprofloxacin with drugs

Ciprofloxacin interacts with mycophenolate mofetil and

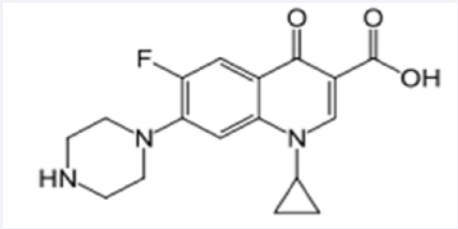

Figure 1 Molecular structure of ciprofloxacin (molecular weight = 331.35 grams/mole).

inhibits its pharmacokinetics [15]. Ciprofloxacin inhibits the pharmacokinetics of diclofenac drops at ocular level [16]. Ciprofloxacin interacts in-vitro with atorvastatin and induces its bioavailability at all pH mediums which are attributed to the formation of charge-transfer complex [17]. A synergistic inhibitory effect of ciprofloxacin and several nonsteroidal anti-inflammatory drugs have been observed on the binding of the neurotransmitter GABA [18]. The pharmacodynamic interaction between ciprofloxacin and GABA inhibitors is extremely poor documented in the spite that this interaction is of clinical importance [19]. Probenecid reduces the renal elimination of ciprofloxacin by inhibiting tubular secretion [20]. The reduction of theophylline clearance by ciprofloxacin is of clinical relevance. The interaction of ciprofloxacin with Mg^{2+}-containing antacids result in tremendous loss of ciprofloxacin bioavailability and this interaction is of therapeutic importance [21]. The co-administration of ciprofloxacin and nonsteroidal anti-inflammatory drugs causes central nervous system toxicity [22]. Significant interactions are the inactivation of ciprofloxacin by antacids and an increase in theophylline blood concentration in the presence of ciprofloxacin [23].

Prophylaxis with ciprofloxacin in children

Ciprofloxacin was found useful for the prophylaxis of lower respiratory-tract infection infants aged ≤ 12 months [24]. Ciprofloxacin prophylaxis reduced 23% fever episodes in children with leukaemia and lymphoma [25]. Ciprofloxacin may be of particularly helpful in the prophylaxis of multidrug-resistant infections that have not responded to standard therapy in immunocompromised children [26]. An oral ciprofloxacin dose of 10 mg/kg thrice-daily may be a suitable alternative antibiotic for the management of sepsis in severely malnourished children [27]. Prophylaxis with ciprofloxacin reduced the hospital duration in children with gam-negative bacteraemia [28].

Treatment with ciprofloxacin in infants and children

Choonara et al. [29] reviewed the literature on the treatment with ciprofloxacin in infants. Clinical response to treatment was estimated at 64% and 91% in two studies with a median of 83% in infants. Of the 14 case reports, 12 yielded positive clinical outcomes and no serious adverse-effects, particularly joint toxicity were observed, although evaluation was predominantly clinical and follow-up was limited to few months after the end of treatment. Thirty infants developed nosocomial Pseudomonas aeruginosa infection and were treated with ciprofloxacin. Two infants (6.6%) died due to the infection and in the remaining 28 infants (93.4%) successfully eradicated the infection. No laboratory abnormality related to ciprofloxacin was observed after one week of follow-up. Ciprofloxacin treatment is effective in life-threatening multidrug-resistant Pseudomonas aeruginosa infections in infants [30]. Forty-one children with cystic fibrosis, aged 2 to 14 years, were treated with ciprofloxacin for an infection caused by Pseudomonas aeruginosa and the treatment extinguished the infection [31]. Ciprofloxacin is the drug recommended by WHO for treatment of dysentery. Ciprofloxacin successfully treated dysentery in children reducing the clinical and bacteriological signs and symptom of dysentery and thus can be expected to decrease diarrhoea mortality attributed to dysentery [32]. The Centers for Disease Control and Prevention recommends a single dose of ciprofloxacin for the treatment of gonorrhoea. Adolescents, aged 15 to 19 years, were treated with a single dose of 500 mg ciprofloxacin for the treatment of uncomplicated gonorrhoea was cured but irreversible cartilage toxicity was observed [33]. Twenty-one children, aged 6 months to 10 years, were suffering from acute diarrhoea and were treated with 10 mg/kg ciprofloxacin intramuscularly twice-daily. Stool cultures revealed the presence of Shigella, Salmonella, Campylobacter species, and diarrheagenic Escherichia coly and ciprofloxacin cured or improved all children [34]. Ciprofloxacin is effective and well tolerated for the treatment of typhoid fever in children. The adverse-effects that are encountered were recorded left no permanent sequelae, and are likely to be caused by the disease itself [35]. Ciprofloxacin has been found to be safe and efficacious in children for the treatment shigellosis cholera and Escherichia coli gastroenteritis in children living in developing countries [36].

In-vitro transfer of ciprofloxacin across the human placenta

In literature there is only one study on the placental transfer of ciprofloxacin and it was reported by Polachek et al. [37]. Only a small fraction of ciprofloxacin passed from the maternal to foetal compartment in-vitro. This fraction is significantly smaller compared to antipyrine indicating that there is a barrier to the transport of ciprofloxacin in human placenta.

Penetration of ciprofloxacin into the beast-milk

Although there are concerns about the possible risk of osteoarticular toxicity with ciprofloxacin, the amounts excreted into the breast-milk are low and studies report no substantial increase in osteoarticular toxicity even with systemic use of ciprofloxacin in the mothers [38]. Ciprofloxacin breast-milk concentrations were: 9.1, 9.1, 9.1, and 6.0 µmol/L at 4, 8, 12, and 16 hours postdose, respectively. These ciprofloxacin concentrations were similar to other published body fluid concentrations following a single oral 500-mg dose [39].

Penetration of ciprofloxacin into the human cerebrospinal fluid (CSF)

A patient with meningitis caused by Pseudomonas aeruginosa was treated with ciprofloxacin intravenously at a dose of 400 mg thrice-daily. Ciprofloxacin concentrations peaked at 10.3 µg/ml whereas the CSF concentration peaked at 0.9 µg/ml. After one week of therapy the microorganism was eradicated and this treatment was found effective [40]. The penetration

of ciprofloxacin into the CSF was investigated in 25 patients with non-inflamed meninges (group A) and in 9 patients with inflamed meninges (group B). In the patients of group A, plasma and CSF were obtained 1 to 10 hours after the second dose of ciprofloxacin and in the patients of group B these samples were obtained 1, 2, 3, 5, 7 and 9 hours after the second dose. In patients of group A, data from were obtained 4, 5 and 6 h post-dose. Mean ciprofloxacin concentrations in the CSF ranged from 0.073 μg/ml to 0.106 μg/ml during this observation time. In patients of group B, ciprofloxacin concentration ranged ranged from 0.089 to 0.260 μg/ml. These results demonstrate that ciprofloxacin diffuses into the CSF at concentrations which exceed the MICs of Neisseria meningitides and most gram-negative aerobic bacilli [41]. Nine patients with external ventriculostomy were treated intravenously with 200 mg of ciprofloxacin twice-daily. Ciprofloxacin elimination half-life ranged from 260 to 430 min in the CSF and that in serum ranged from 145 to 170 min. Post-dose concentration in CSF at 60 min ranged from 0.042 to 0.223 (median, 0.110). Thus ciprofloxacin therapy of the central nervous system may be inadequate when only minor impairment of the blood-CSF barrier exists [42]. Twenty-three patients with meningitis or ventriculitis were treated intravenously with 200 mg of ciprofloxacin twice-daily. Ciprofloxacin concentration in CSF were measured on four occasions ranging from 60 to 400 min after dosing and ranged from 0.35 to 0.56 μg/ml. These concentrations were equal or higher the MICs of most enterobacteria [43].

Treatment of meningitis with ciprofloxacin in infants and children

Ciprofloxacin added to a third-generation cephalosporin at least offer advantage for neurologic outcome and mortality in infants with Escherichia coli meningitis [44]. Ciprofloxacin and meropenem should be considered the antibiotic treatment options for the meningitis caused by Citrobacter kosen in infants [45]. Ciprofloxacin was administered intravenously at a dose of 60 mg/kg daily to 4 newborn infants, aged 21 to 28 days, and to 8 infants aged 2 to 6 months. Subjects had meningitis caused by Escherichia coli, Salmonella Enteritidis, Acinetobacter species, Haemophilus influenzae, Staphylococcus epidermidis, Staphylococcus aureus and Enterococcus faecalis. Ten cases were cured and in two cases, reversible hydrocephalus appeared that responded to intraventricular punctures [46]. Preterm infants with meningitis caused by bacteria resistant to conventional antibiotics were treated with ciprofloxacin and the meningitis was cured without severe adverse-effects [47]. Infants had meningitis caused by Salmonella paratyphi which was resistant to ceftazidime and cefotaxime whereas the organism was eradicated by ciprofloxacin [48]. Four children had meningitis caused by multidrug-resistant organisms. Intraventricular ciprofloxacin treated meningitis in these children [49]. Two children, aged < 1 year, had the meningitis caused by Salmonella meningitis. Ciprofloxacin had a cure-rate of 88.9% whereas chloramphenicol, ampicillin, and cotrimoxazole had a cure-rate of 41.2% and the relapse-rate was 11.8%. Ciprofloxacin is the drug of choice to treat meningitis caused by this organism in children [50]. Children had meningitis caused by Salmonella meningitis which was resistant to imipenem, ceftriaxone, cotrimoxazole and chloramphenicol. A combination of ciprofloxacin with cefotaxime or with ciprofloxacin or with ceftriaxone cured the meningitis in children [51].

DISCUSSION

Ciprofloxacin is a fluoroquinolone and its introduction in clinical use represents a particularly important therapeutic advance. Ciprofloxacin is active against gram-positive and gram-negative organisms. Ciprofloxacin targets bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria, topoisomerase IV is the primary target. In contrast, DNA gyrase is the primary quinolone target in many gram-negative microbes. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling at concentrations that correlate well with those required to inhibit bacterial growth. Ciprofloxacin is active against Proteus, Escherichia coli, Klebsiella, Chlamydia, Mycoplasma, Legionella, Brucella and Salmonella, Shigella, Enterobacter, Campylobacter, Mycobacterium species [1]. Ciprofloxacin may be administered orally and intravenously, and following oral dosing it is rapidly absorbed. Ciprofloxacin is usually administered twice-daily for the treatment of different infections whereas a single oral dose is used to treat gonorrhoea and to prevent meningococcal meningitis [2]. Ciprofloxacin has been found efficacy and safe in infants and children [3-8]. In particular, it has found efficacy and safe in neonates with sepsis [3] and in infected children [4-8]. Ciprofloxacin induces adverse-effects in infants and children [9-11]. The major adverse-effects are musculoskeletal abnormalities [9], cartilage toxicity [10], abnormal liver function test, arthropathy, and nausea but all the adverse-effects resolved [11]. Following an oral administration, ciprofloxacin is rapidly absorbed and the absorption half-life is 0.40 and 0.29 hours in infants and in children, respectively. The elimination half-life is 2.73 and 1.28 hours (P-value = 0.001) in infants and children, respectively. AUC and the mean residence time are greater in infants and children and these results indicate that ciprofloxacin is eliminated more slowly in infants because this drug is mainly eliminated by renal route and renal function increases with infant maturation and child development [13]. Consisting with these results, the total body clearance and the distribution volume of ciprofloxacin increase with child ageing whereas the elimination half-life decreases with child age [14]. Ciprofloxacin interacts with drugs [15-23]. This antibiotic inhibits the pharmacokinetics of mycophenolate mofetil [15] and that of diclofenac at ocular level [16], reduces the bioavailability of atorvastatin in-vitro [17]. Ciprofloxacin and nonsteroidal anti-inflammatory drugs inhibit the binding of GABA [18] and ciprofloxacin inhibits the tubular excretion of probenecid [19], the clearance of theophylline [20], the co-administration of Mg^{2+}-containing antacids inhibit the ciprofloxacin bioavailability [21]. Ciprofloxacin co-administered with antacids causes neurologic toxicity [22], and increase theophylline blood concentration [23]. Prophylaxis with ciprofloxacin was used to prevent lower respiratory-tract infection [24], to reduce fever episodes in children with leukaemia and lymphoma [25], to prevent multidrug-resistant infections [26], sepsis in malnourished children [27], and reduced children hospital stay [28]. Treatment with ciprofloxacin has been assessed in infants and children [29-36]. Ciprofloxacin eradicated Pseudomonas aeruginosa in infants and children [29-31], cured dysentery [32], gonorrhoea [33], eradicated Shigella, Salmonella, Campylobacter species, and

diarrheagenic Escherichia coli from stool [34], cured typhoid fever [35], shigellosis cholera and gastroenteritis caused by Escherichia coli [36]. Ciprofloxacin poorly crosses the human placenta [37] and poorly penetrate into the breast-milk [39-39]. In contrast, significant amounts of ciprofloxacin penetrates into the cerebrospinal fluid [40-43] and cured meningitis in infants caused by Escherichia coli [44], Citrobacter kosen [45], by Escherichia coli, Salmonella enteritidis, Acinetobacter species, Haemophilus influenzae, Staphylococcus species and Enterococcus faecalis [46], caused by multidrug-resistant organisms [47] and by Salmonella paratyphi [48]. Ciprofloxacin cured the meningitis caused multidrug-resistant organisms [49], by Salmonella meningitis [50], and a combination of ciprofloxacin with cefotaxime or ciprofloxacin cured meningitis caused by Salmonella meningitis which was resistant to imipenem, ceftriaxone, cotrimoxazole and chloramphenicol [51] in children.

In conclusion, ciprofloxacin is a fluoroquinolone and targets bacterial DNA and topoisomerase IV. For many gram-positive bacteria, topoisomerase IV is the primary target. In contrast, DNA gyrase is the primary quinolone target in many gran-negative organisms. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling that can occur during DNA replication. Ciprofloxacin is active against Proteus, Escherichia coli, Klebsiella, Chlamydia, Mycoplasma, Legionella, Brucella and Salmonella, Shigella, Enterobacter, Campylobacter, Mycobacterium species [1]. Ciprofloxacin may be administered orally and intravenously, and following oral dosing it is rapidly absorbed. The absorption half-life is 0.40 and 0.28 hours in infants and children, respectively, and the elimination half-life is 2.73 and 1.28 hours, (P-value < 0.001) in these subjects, respectively. The longer elimination half-life in infants is due to a lower renal function as ciprofloxacin is mainly eliminated by renal route. Ciprofloxacin has been found efficacy and safe in infants and children but may cause adverse-effects and the major adverse-effect is arthropathy which resolves after therapy. Prophylaxis has been found useful in children to prevent infection and treatment has been assessed in infants and children. Ciprofloxacin poorly crosses the human placenta and poorly penetrate into the breast-milk. In contrast, it reaches significant amounts into the cerebrospinal fluid and successfully cured meningitis caused by different bacteria in infants and children. The aim of this study is to review the clinical pharmacology of ciprofloxacin in infants and children.

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