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Review Article

Clinical Pharmacology of Ciprofloxacin in Infants and Children

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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 for many gram-negative bacteria. Ciprofloxacin inhibits gyrase-mediated DNA supercoiling at concentrations that correlate with those required to inhibit bacterial growth (0.1 to 10 µg/ml). Ciprofloxacin is active against Proteus, Escherichia coli, Klebsiella, Salmonella, Shigella, Enterobacter, Campylobacter, Chlamydia, Mycoplasma, Legionella, Brucella, Mycobacterium tuberculosis, Mycobacterium fortuitum, and Mycobacterium kansasii. Ciprofloxacin is rapidly absorbed following oral administration and the mean elimination half-life of ciprofloxacin is 16.6, 6.2, 4.2, and 3.3 hours in newborns, infants, children, and adolescents, respectively. Ciprofloxacin is eliminated mainly by renal route and the renal function increases with infant maturation and child development. Ciprofloxacin has been found efficacy and safe in infants and children but can cause adverse-effects and the major adverse-effect is arthropathy which resolves with therapy. Ciprofloxacin interacts with drugs. Prophylaxis with ciprofloxacin prevents bacterial infections and ciprofloxacin treats bacterial infections in infants and children. Ciprofloxacin penetrates into the cerebrospinal fluid in significant amounts and successfully treats bacterial meningitis in infants and children and ciprofloxacin poorly crosses the human placenta and poorly penetrates into the beast-milk. The aim of this study is to review published data on ciprofloxacin dosing, efficacy and safely, adverse-effects, pharmacokinetics, interaction with drugs, prophylaxis, treatment, penetration into the cerebrospinal fluid, treatment of meningitis in infants and children and ciprofloxacin transfer across the human placental, and migration into the breast-milk.

Key words: cerebrospinal-fluid; ciprofloxacin; dosing; efficacy-safely; drug-interaction; meningitis; pharmacokinetics; prophylaxis; and treatment

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, which separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication, 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 (0.1 to 10 µg/ml). Mutation of the gene that encodes the A subunit of the gyrase can confer resistance to 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].

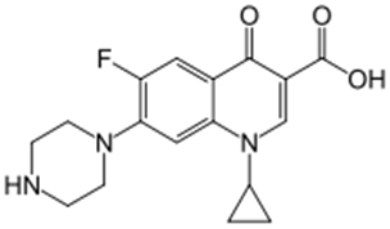
Antimicrobial activity of ciprofloxacin

Ciprofloxacin is a potent bactericidal agent against most gram-negative pathogens when first introduced, including Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter and Campylobacter. Ciprofloxacin has sufficient activity against Pseudomonas species 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. 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 (including Mycobacterium tuberculosis). Ciprofloxacin has activity against

Mycobacterium fortuitum, Mycobacterium kansasii, and Mycobacterium tuberculosis [1].

Absorption, distribution, metabolism and excretion of ciprofloxacin

Ciprofloxacin's bioavailability is approximately 70%. Typically oral doses are 250 to 750 mg and intravenous doses are 200 to 400 mg twice-daily. The elimination half-life of ciprofloxacin is about 5 hours, and the drug is typically dosed twice-daily, with the exception an extended-release formulation, which can be doses once-daily. 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, and macrophages and neutrophils higher than in serum concentrations. 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 [1].



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

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, safely infants, children", "ciprofloxacin adverse-effects infants, children", "ciprofloxacin pharmacokinetics infants, children", "ciprofloxacin drug interaction", "ciprofloxacin prophylaxis infants, children", "ciprofloxacin treatment infants, children", "ciprofloxacin CSF", "ciprofloxacin meningitis infants, children", "ciprofloxacin placental transfer", and "ciprofloxacin breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1] and the British National Formulary for Children [2] have been consulted.

Results

Administration schedules of ciprofloxacin to infants and children [2]

Oral or intravenous administration of ciprofloxacin to infants

Oral treatment of infants with severe respiratory-tract infections and gastrointestinal infections

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

Intravenous treatment of infants with severe respiratory-tract infections and gastrointestinal infections

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 of ciprofloxacin to children

Oral treatment for Fistulating Crohn's disease

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

Oral treatment of severe respiratory-tract infections and gastrointestinal infections

Children. Give: 20 mg twice-daily (maximum per dose = 750 mg).

Oral treatment of pseudomonal lower respiratory-tract infection in cystic fibrosis

Children. Give: 20 mg/kg twice-daily (maximum per dose = 750 mg).

Intravenous treatment of pseudomonal lower respiratory-tract infection in cystic fibrosis

Children. Give: 10 mg/kg thrice-daily (maximum per dose = 450 mg) to be given over 60 min of infusion.

Intravenous treatment of children with 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.

Oral 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).

Intravenous treatment for complicated urinary-tract infections

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 uncomplicated gonorrhoea (when sensitivity is confirmed in combination with azithromycin).

Children aged 13 to 15 years. Give: 500 mg for 1 dose.

Oral treatment of uncomplicated gonorrhoea (genital and pharyngeal infection, when the sensitivity is confirmed).

Children aged 16 to 17 years. Give: 500 mg for 1 dose.

Intravenous treatment of disseminated gonococcal infection (when the sensitivity is confirmed)

Children aged 16 to 17 years. Give: 500 mg twice-daily for 7 days, the treatment may be switched for 24 to 48 hours after symptoms improve to a suitable oral antibacterial.

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

Oral treatment of acute pyelonephritis or urinary-tract infection (catheter associated)

Children aged 16 to 17 years. Give: 500 mg twice-daily for 7 days.

Intravenous treatment of acute pyelonephritis or urinary-tract infection (catheter associated)

Children aged 16 to 17 years. Give: 400 mg thrice-daily or twice-daily for 7 days.

Efficacy and safely of ciprofloxacin in infants and children

Ciprofloxacin was administered orally at a daily dose of 15 mg/kg for 10 days to newborns with sepsis and this treatment effectively and safely treats the sepsis [3]. Ciprofloxacin was administered orally at a daily dose of 10 to 20 mg/kg for 12 days to 9 children with bacterial infection and this treatment effectively and safely treats the bacterial infection [4]. Ciprofloxacin administered orally at a daily dose of 20 mg/kg for 14 days to 56 burn children with bacterial infection effectively and safely treats the bacterial infection and does not cause arthropathy [5]. Ciprofloxacin administered orally at a daily dose of 15 to 25 mg/kg for 9 to 16 days to 58 children, aged 8 months to 13 years, with bacterial infection effectively and safely treats the bacterial infection and does not cause arthropathy [6]. Ciprofloxacin administered orally at a daily dose of 15 mg/kg for 10 days to children with bacterial infection effectively and safely treats the bacterial infection and the adverse-effects were noted in only 5% to 15% of children. The most common adverse-effects were: gastrointestinal, skin, and central nervous system reactions, and reversible arthralgia occurred in only 36 out of 1,113 children (3.2%) with cystic fibrosis, and no cartilage damage was demonstrated by radiographic procedures [7]. Six-hundred-thirty infants and children, aged 3 days to 17 years, with respiratory-tract infection and acute pulmonary acerbation received ciprofloxacin orally at a median daily dose of 25.2 mg/kg and the median duration of therapy was 22.8 days. This treatment effectively and safely treats infants and children and reversible arthralgia occurred in only 8 infants and children (1.3%) which resolved after cessation of treatment [8].

Adverse-effects caused by ciprofloxacin in infants and children

One-hundred-eight-four paediatric patients, aged ≤ 17 years, were treated with ciprofloxacin orally at a daily dose ranging from 3.1 to 93.8 mg/kg or intravenously at a daily dose ranging from 3.2 to 76.9 mg/kg. The most common adverse-effects were: musculoskeletal adverse-effects, abnormal liver function tests, nausea, changes in white blood cell counts and vomiting. Musculoskeletal adverse-effects occurred in only 1.4% of children and arthralgia accounted for 50% of the musculoskeletal adverse-effects and all cases of arthropathy resolved or improved with management [9]. A single oral dose of 500 mg of ciprofloxacin was administered to 5,236 infants, children, and adolescents, aged 5 days to 24 years, and the only adverse-effect noted is reversible cartilage toxicity [10]. Choonara [11] reviewed the adverse-effects caused by ciprofloxacin in children aged ≤ 17 years. One-hundred-five articles were reviewed and involved 16,184 paediatric patients. There were 1,065 adverse-effects (risk 7%, 95% confidence interval = 3.2% to 14.0%) and the most common adverse-effects were: musculoskeletal, abnormal liver function test, nausea, change in white cell count, and vomiting. Ciprofloxacin related death occurred in only a newborn infant. The musculoskeletal adverse-effects were 258 which occurred in 232 paediatric patients (1.4%). Arthralgia accounted for 50% of the musculoskeletal adverse-effects and the age of occurrence of arthropathy ranged from 7 months to 17 years (median, 10 years) and all cases of 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), a postnatal age of 27.0 days (range, 5.0 to 121), and a 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 twice-daily to infants with longer postmenstrual age (16%). 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). Ciprofloxacin was administered to infants infected by Enterobacter species resistant to standard treatment and also to infants at risk of meningitis. Table 1 summarizes the pharmacokinetic parameters of ciprofloxacin.

	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

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.

Table 1. Pharmacokinetic parameters of ciprofloxacin which have been obtained in 60 infants with median postmenstrual, postnatal ages, body-weight and serum creatinine of 27.9 weeks, 27.0 days, 1,955 grams, and 42 µmol/L, respectively. 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 (16%) in infants with longer postmenstrual age. Values are by Zhao et al. [12].

This table shows that the central distribution volume is higher than the water volume and is similar to the peripheral volume indicating that ciprofloxacin distributes into the whole body and there is a remarkable interindividual variability in the pharmacokinetic parameters. This variability is accounted by the wide variation in postmenstrual age, postnatal age, and body-weight of infants included in the study.

Pharmacokinetics of ciprofloxacin in infants and young children

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

Subjects	Peak conc. (µg/ml)	Time to peak conc. (h)	Absorption half-life (h)	Elimination half-life (h)	$AUC_{0-\infty}$ (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

*Student t test for unimpaired data. AUC = area under the concentration-time curve.

Table 2. Pharmacokinetic parameters of ciprofloxacin which have been obtained in 7 infants and in 9 young children. A single oral dose of 15 mg/kg of ciprofloxacin was administered to all subjects. Values are the mean±SD, by Peltola et al. [13].

This table shows that the peak concentration, the time to reach the peak concentration, and the absorption half-life of ciprofloxacin are similar in infants and in young children. In contrast, the elimination half-life, the area under the concentration-time curve, and the mean residence time of ciprofloxacin are higher in infants suggesting that ciprofloxacin is more slowly eliminated in infants than in young children. Ciprofloxacin is eliminated mainly by renal route and the renal function increases with infant maturation and child maturation thus the elimination half-life of ciprofloxacin is longer in infants than in young children and consequently

the area under the concentration-time curve and the mean residence time of ciprofloxacin are higher in infants than in young children.

Pharmacokinetics of ciprofloxacin in infants, children, and adolescents

Payen et al. [14] investigated the pharmacokinetics of ciprofloxacin in 3 newborns 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 13), and in 8 adolescents, aged 16.4 years (range, 12 to 24) and weighing 42.3 kg (range, 28 to 58). Thirteen children (48.1%) and 7 adolescents (87.5%) were suffering from cystic fibrosis. Fifteen children (63.0%) 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. A single intravenous infusion of 10 mg/kg of ciprofloxacin was administered to all subjects and it was followed by ciprofloxacin administered orally at a dose of 15 mg/kg twice-daily to 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 8 to 15 mg/kg twice-daily. Table 3 summarizes the pharmacokinetic of ciprofloxacin obtained in infants, children, and adolescents.

Group (age) and parameter	Total body clearance (L/h)	Elimination half-life (h)	Distribution volume (L)
Newborns 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
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

Table 3. Pharmacokinetic parameters of ciprofloxacin which have been obtained in 3 newborns, 17 infants, 27 children, and 8 adolescents. Values are the minimum, the maximum, and the %coefficient of variation, by Payen et al. [14].

This table shows that the total body clearance and the distribution volume of ciprofloxacin increase with increasing the subject age whereas the elimination half-life of ciprofloxacin decreases with increasing the subject age. Ciprofloxacin is eliminated mainly by renal route and the renal function increases with infant maturation and child development thus the elimination half-life of ciprofloxacin decreases with increasing the subject age. Ciprofloxacin distributes in the whole body (see table 1) thus the distribution volume of ciprofloxacin increases with increasing the body-weight. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the wide variability in subject age and body-weight.

Interaction of ciprofloxacin with drugs

Ciprofloxacin interacts with mycophenolate mofetil and ciprofloxacin reduces the area under the concentration-time curve of mycophenolate mofetil as ciprofloxacin improves the elimination of mycophenolate mofetil [15]. Ciprofloxacin interacts with diclofenac and reduces the availability of diclofenac drops at ocular level [16]. The co-administration of atorvastatin with ciprofloxacin leads to the formation of a charge-transfer complex which depletes the binding of these drugs to their respective receptors [17]. The co-administration of ciprofloxacin with nonsteroidal anti-inflammatory drugs reduces the binding of the neurotransmitter GABA in brain causing an epileptogenic effect [18]. Ciprofloxacin inhibits the metabolism of caffeine, theophylline and antipyrine [19]. Ciprofloxacin interacts with theophylline and ciprofloxacin reduces the clearance of theophylline [20]. Ciprofloxacin interacts with theophylline and ciprofloxacin increases the blood concentration of theophylline [21]. Probenecid reduces the renal elimination of ciprofloxacin by inhibiting the tubular secretion of ciprofloxacin [22]. The absorption of ciprofloxacin is significantly reduced when ciprofloxacin is co-administered with antacids containing magnesium and/or aluminium and this concomitant administration must be avoided [23].

Prophylaxis with ciprofloxacin in children

The prophylaxis with ciprofloxacin reduces pneumonia, lung exacerbations, length of hospital stay and mortality in high-risk children [24]. The prophylaxis with ciprofloxacin reduces the occurrence of fever in children with leukaemia and lymphoma [25]. The prophylaxis with ciprofloxacin is particularly helpful in preventing multidrug-resistant infections which do not

respond to standard antibiotic therapy in immunocompromised children [26]. The prophylaxis with ciprofloxacin administered orally at a dose of 10 mg/kg thrice-daily prevents sepsis in severely malnourished children [27]. The prophylaxis with ciprofloxacin reduces the length of hospital stay in children with gam-negative bacteraemia [28].

Treatment of bacterial infections with ciprofloxacin in infants and children

Kaguelidou et al. [29] reviewed the literature about the treatment of bacterial infection with ciprofloxacin in infants and children. A study showed that the bacterial infection was treated with ciprofloxacin in 64% of infants, another study showed that ciprofloxacin treats bacterial infection in 91% of infants, and another study showed that ciprofloxacin treats bacterial infections in 83% of infants. Fourteen reports indicate that ciprofloxacin treats bacterial infections in infants and no serious adverse-effects, particularly joint toxicity, were observed. Thirty infants developed nosocomial infection caused by Pseudomonas aeruginosa and were treated with ciprofloxacin intravenously at an initial dose of 10 mg/kg and the daily dose was increased to 40 mg/kg according to the clinical response. Two infants (6.6%) died due to the infection and in the remaining 28 infants (93.4%) the infective agent was eradicated. No laboratory abnormality related to ciprofloxacin was observed after one week of follow-up. Ciprofloxacin administered orally at a dose of 15 mg/kg twice-daily for 10 days effectively treats life-threatening infections caused by a multidrug-resistant Pseudomonas aeruginosa in infants [30]. Forty-one children with cystic fibrosis, aged 2 to 14 years, were treated with ciprofloxacin orally at a dose of 20 mg/kg twice-daily for 10 days to treat an infection caused by Pseudomonas aeruginosa and this treatment eradicated the infective agent [31]. Ciprofloxacin is the drug recommended by WHO for treatment of dysentery. Ciprofloxacin administered intravenously at a dose of 20 mg/kg twice-daily for 10 days successfully treats dysentery in children reducing the clinical and bacteriological signs and symptom of dysentery thus ciprofloxacin decreases the mortality due to dysentery [32]. The Centers for Disease Control and Prevention recommends a single oral dose of ciprofloxacin for the treatment of gonorrhoea. Adolescents, aged 15 to 19 years, were treated with a single oral dose of 500 mg ciprofloxacin for the treatment of uncomplicated gonorrhoea which 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 ciprofloxacin intramuscularly at a dose of 10 mg/kg twice-daily for 10 days. Stool cultures revealed the presence of Shigella, Salmonella, Campylobacter species, and diarrheagenic Escherichia coly and ciprofloxacin cures or improves all children [34]. Eighteen children had positive cultures for Salmonella typhi and 3 children had positive cultures for Salmonella paratyphi A and all children received ciprofloxacin intravenously at a median daily dose of 15 mg/kg and the treatment lasted 10 days. Ciprofloxacin was well-tolerated and effectively treats of typhoid fever and the few adverse-effects that were recorded left no permanent sequelae and were likely to be caused by the disease itself [35]. Ciprofloxacin administered intravenously at a dose of 20 mg/kg twice-daily for 15 days has been found to be a safe and efficacious treatment of shigellosis cholera and Escherichia coli gastroenteritis in children living in developing countries [36].

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 for 12 days. At the end of therapy, the peak concentration of ciprofloxacin was 10.3 μg/ml in plasma and 0.9 μg/ml in the CSF. After one week of treatment the microorganism was eradicated from the CSF and this treatment was found effective [37]. The penetration of ciprofloxacin into the CSF has been investigated in 25 patients with non-inflamed meninges (group A) and in 9 patients with inflamed meninges (group B) and all patients received ciprofloxacin intravenously at a dose of 200 mg twice-daily for 10 days. In patients of group A, CSF specimens were sampled from 1 to 10 hours after the second dose of ciprofloxacin and in patients of group B specimens of CSF were sampled 1, 2, 3, 5, 7 and 9 hours after the second dose of ciprofloxacin. In patients of group A, ciprofloxacin concentrations in the CSF ranged from 0.073 to 0.106 μg/ml and in patients of group B, ciprofloxacin concentration ranged ranged from 0.089 to 0.260 μg/ml. These results indicate that ciprofloxacin penetrates into the CSF in concentration which exceeds the minimum inhibitory concentration (MIC) of Neisseria meningitides and gram-negative aerobic bacilli which were the bacteria that cause the meningitis [38]. Nine patients with external ventriculostomy received ciprofloxacin by intravenous infusion at a dose of 200 mg twice-daily for 10 days. The CSF concentration of ciprofloxacin peaked at 60 to 120 min after the end of the infusion. Ciprofloxacin elimination half-life ranged from 260 to 430 min in the CSF and from 145 to 170 min in serum. At 60 min post-dose the ciprofloxacin concentration in CSF ranged from 0.042 to 0.223 μg/ml (median, 0.110). This concentration is lower than the MIC_{90} of bacteria involved in central nervous system infections (CNS) thus this concentration is inadequate to treat bacteria which cause infection in the CNS [39]. Of 23 hospitalized patients, 20 patients (86.9%) had purulent meningitis and 3 patients (13.1%) had ventriculitis and all patients and were treated with ciprofloxacin intravenously at a dose of 200 mg twice-daily for 14 days. Ciprofloxacin concentration in CSF was measured on four occasions ranging from 60 to 480 min after dosing and ranged from 0.35 to 0.56 μg/ml. These concentrations were equal or higher the MICs of enterobacteria causing the meningitis or the ventriculitis [40].

Treatment of bacterial meningitis with ciprofloxacin in infants and children

Three-hundred-sixty-seven infants, aged from 1 month to < 12 months, had the meningitis caused by Escherichia coli and had a median postnatal age of 15 days (range, 1 to 318) and a median body-weight of 3.42 kg (range, 0.66 to 9.4). Eight-six infants (23.4%) presented neurologic complications (seizures, strokes, empyema, abscesses, or hydrocephalus). Two-hundred-one infants (54.8%) received ciprofloxacin intravenously at a median daily dose was 30 mg/kg (range, 10 to 60) and 166 infants (45.2%) also received a third generation cephalosporin intravenously. Ciprofloxacin added to a third generation cephalosporin at least offers no advantage for neurologic outcome and mortality in infants with meningitis caused by Escherichia coli [41]. A preterm infant had the meningitis caused by Citrobacter koseri and was treated with intravenous ciprofloxacin administered at a daily dose of 10 to 20 mg/kg plus cefotaxime administered intravenously at a daily dose of 100 mg/kg and the treatment lasted 21 days. Ciprofloxacin and cefotaxime should be considered the treatment of choice for treatment of meningitis caused by Citrobacter koseri [42]. Ciprofloxacin was administered intravenously at a daily dose of 10 to 60 mg/kg to 4 newborns, aged 21 to 28 days, and to 8 infants aged 2 to 6 months. Six subjects (50.0%) presented a meningitis caused by gram-negative organisms: Escherichia coli (2), Salmonella enteritidis (1), Acinetobacter calcoaceticus (1), two infants had the meningitis caused by 2 organisms, and (Haemophilus influenzae plus Staphylococcus epidermidis or Acinetobacter species plus Staphylococcus epidermidis), and 6 subjects (50.0%) had a meningitis caused by gram-positive cocci (Staphylococcus aureus in 4 subjects and Enterococcus faecalis in 2 subjects). Ten subjects (83.3%) were cured and two subjects (16.7%) had reversible hydrocephalus which responded to the treatment [43]. Twenty-eight preterm infants or low-birth-weight infants with meningitis caused by Enterobacter cloacae received ciprofloxacin intravenously at a daily dose of 4 to 40 mg/kg and the peak concentration of ciprofloxacin in serum ranged from 0.98 to 5.7 μg/ml and the peak concentration of ciprofloxacin in the cerebrospinal fluid ranged from 0.10 to 1.45 μg/ml. Ciprofloxacin effectively treats preterm or low-birth-weight infants with the meningitis caused by Enterobacter cloacae and does not cause severe adverse-effects [44]. A breast-fed infant had meningitis caused by Salmonella paratyphi A which was resistant to ceftazidime and cefotaxime whereas this organism was eradicated by ciprofloxacin [45]. Five children had the meningitis caused by Klebsiella pneumoniae, Pseudomonas aeruginosa or by Enterococcus faecium which were multidrug-resistant. Children were treated with ciprofloxacin intravenously at a daily dose of 20

to 40 mg/kg for 14 to 21 days and this treatment eradicated the bacteria from the cerebrospinal fluid [46]. Twenty children, aged < 1 year, had the meningitis caused by Salmonella typhimurium and received either ciprofloxacin intravenously or chloramphenicol, ampicillin, and clotrimazole intravenously. The cure-rate was 88.9% in children who received ciprofloxacin and 41.2% in children who received chloramphenicol, ampicillin, and cotrimoxazole. Ciprofloxacin is the drug of choice for treatment of meningitis caused by Salmonella typhimurium in children [47]. Two children, aged 8 and 9 years, had meningitis caused by Salmonella meningitis which was resistant to imipenem, ceftriaxone, cotrimoxazole and chloramphenicol whereas ciprofloxacin administered intravenously at a daily dose of 15 to 30 mg/kg treated the meningitis [48].

In-vitro transfer of ciprofloxacin across the human placenta

In literature there is only one study on the transfer of ciprofloxacin across the human placenta and has been reported by Polachek et al. [49]. The ratio of the concentration of ciprofloxacin in the foetal compartment to that in the maternal compartment is only 3.2±0.7% indicating that ciprofloxacin is poorly transferred across the human placenta.

Penetration of ciprofloxacin into the beast-milk

Ten lactating women received 3 oral doses of 750 mg twice-daily of ciprofloxacin and the highest average concentration of ciprofloxacin in milk is 3.79 μg/ml at two hours after dosing. The concentration of ciprofloxacin in milk is 0.20 and 0.02 μg/ml 12 and 24 hours, respectively, after dosing [50]. A lactating woman received a single oral dose of 500 mg of ciprofloxacin and the concentration of ciprofloxacin in milk is: 9.1, 9.1, 9.1, and 6.0 μmol/L at 4, 8, 12, and 16 hours after dosing, respectively [51]. These results indicate that ciprofloxacin poorly migrates into the breast-milk.

Discussion

Ciprofloxacin is a fluoroquinolone and its introduction in clinical use represents a particularly important therapeutic advance. Ciprofloxacin has a broad antimicrobial activity and is active after oral administration for treatment of a wide variety of infectious diseases. Ciprofloxacin targets bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria, topoisomerase IV, which separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication, 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 (0.1 to 10 μg/ml). 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 enzymes. Ciprofloxacin is a potent bactericidal agent against most gram-negative pathogens including Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter, Campylobacter, and Pseudomonas. 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 (including Mycobacterium tuberculosis). Ciprofloxacin has activity against Mycobacterium fortuitum, Mycobacterium kansasii, and Mycobacterium tuberculosis [1]. The administration schedules of ciprofloxacin have been reported in infants and children, ciprofloxacin may be administered orally and intravenously, and following oral administration is rapidly absorbed. Ciprofloxacin is usually administered twice-daily or thrice-daily for the treatment of different infections whereas a single oral dose is used to prevent secondary case of meningococcal meningitis in infants and to treat uncomplicated gonorrhoea in children [2]. The efficacy and safely of ciprofloxacin have been reviewed in infants and children. Ciprofloxacin was administered orally at a daily dose of 15 mg/kg for 10 days to newborns with sepsis and this treatment effectively and safely treats the sepsis [3], ciprofloxacin was administered orally at a daily dose of 10 to 20 mg/kg for 12 days to 9 children with bacterial infection and this treatment effectively and safely treats the bacterial infection [4], ciprofloxacin administered orally at a daily dose of 20 mg/kg for 14 days to burn children with bacterial infection effectively and safely treats the bacterial infection and does not cause arthropathy [5], ciprofloxacin administered orally at a daily dose of 15 to 25 mg/kg for 9 to 16 days to children with bacterial infection effectively and safely treats the bacterial infection and does not cause arthropathy [6], ciprofloxacin administered orally at a daily dose of 15 mg/kg for 10 days to children with bacterial infection effectively and safely treats the bacterial infection and the adverse-effects were noted in only 5% to 15% of children. The most common adverse-effects are: gastrointestinal, skin, and central nervous system reactions and reversible arthralgia occurs in only 3.2% of children with cystic fibrosis and no cartilage damage is observed [7], infants and children, aged 3 days to 17 years, with respiratory-tract infection and acute pulmonary acerbation received ciprofloxacin orally at a median daily dose of 25.2 mg/kg for a median duration of 22.8 days. This treatment effectively and safely treats the children and reversible arthralgia occurs in only 1.3% of infants and children [8]. These results indicate that ciprofloxacin effectively and safely treats bacterial infections in infants and children and induces few adverse-effects. The adverse-effects caused by ciprofloxacin have been reviewed. Ciprofloxacin was administered orally at a daily dose ranging from 3.1 to 93.8 mg/kg or intravenously at a daily dose ranging from 3.2 to 76.9 mg/kg to children aged ≤ 17 years and the most common adverse-effects are: musculoskeletal adverse-effects, abnormal liver function tests, nausea, changes in white blood cell counts and vomiting. Musculoskeletal adverse-effects occurs in only 1.4% of children and arthralgia accounts for 50% of the musculoskeletal adverse-effects and all cases of arthropathy resolve or improve with management [9], a single oral dose of 500 mg of ciprofloxacin was administered to infants, children, and adolescents and the only adverse-effect noted is reversible cartilage toxicity [10]. Choonara [11] reviewed the adverse-effects caused by ciprofloxacin in children aged ≤ 17 years and the most common adverse-effects are: musculoskeletal, abnormal liver function test, nausea, change in white cell count, and vomiting. Death related to ciprofloxacin treatment occurred in only a newborn and musculoskeletal adverse-effects occur in only 1.4% of children. Arthralgia accounts for 50% of the musculoskeletal adverse-effects and the age of occurrence of arthropathy ranged from 7 months to 17 years (median, 10 years) and all cases of arthropathy resolve or improve with management. Zhao et al. [12] studied the pharmacokinetics of ciprofloxacin in 60 infants with a median postmenstrual age of 36.5 weeks, a postnatal age of 27.0 days and a body-weight of 1,115 grams and 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 twice-daily to infants with longer postmenstrual age (16%). Ciprofloxacin was administered to infants infected by Enterobacter species resistant to standard treatment and also to infants at risk of meningitis. The median central and peripheral distribution volume of ciprofloxacin is 1.82 and 1.97 L, respectively, indicating the ciprofloxacin distributes into the whole body. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the wide variation in postmenstrual age, postnatal age, and body-weight of infants included in the study. Peltola et al. [13] studied the pharmacokinetics of ciprofloxacin in 7 infants, aged 5 to 14 weeks, and in 9 children, aged 1 to 5 years, and a single oral dose of 15 mg/kg of ciprofloxacin was administered to all subjects who were infected by Salmonella typhi. Ciprofloxacin is rapidly absorbed following oral administration, the absorption half-life is 0.40 and 0.29 hours (P-value > 0.05) in infants and in young children, respectively, and ciprofloxacin is rapidly eliminated as the elimination half-life is 2.73 and 1.28 hours (P-value < 0.001) in infants and young children, respectively. The peak concentration, the time to reach the peak concentration, and the absorption half-life of ciprofloxacin are similar in infants and in young children. In contrast, the elimination half-life, the area under the concentration-time curve, and the mean residence time of

ciprofloxacin are significantly higher in infants than in young children. Ciprofloxacin is eliminated mainly by renal route and the renal function increases with infant maturation and child development thus the elimination half-life of ciprofloxacin is longer in infants than in young children and consequently the area under the concentration-time curve and the mean residence time of ciprofloxacin are higher in infants than in children. Payen et al. [14] studied the pharmacokinetics of ciprofloxacin in 3 newborns aged 1.1 to 2.2 days, in 17 infants aged 28 days to 23 months, in 27 children aged 2 to 11 years, and in 8 adolescents aged 12 to 24 years. Thirteen children (48.1%) and 7 adolescents (87.5%) were suffering from cystic fibrosis and 15 children (63.0%) had dysuria or polyuria. A single intravenous infusion of 10 mg/kg of ciprofloxacin was administered to all subjects and it was followed by ciprofloxacin administered orally at a dose of 15 mg/kg twice-daily to 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 a fourth group of subjects, aged 1 day to 4 years, received ciprofloxacin intravenously at a dose of 8 to 15 mg/kg twice-daily. The mean elimination half-life of ciprofloxacin is 16.6, 6.2, 4.2, and 3.3 hours in newborns, infants, children, and adolescents, respectively, indicating that the elimination half-life of ciprofloxacin decreases with increasing the subject age. Consisting with these results the total body clearance of ciprofloxacin increases with the subject age. The distribution volume of ciprofloxacin increases with the body-weight and this result is consisting with the observation that ciprofloxacin distributes into the whole body (see above). The interaction of ciprofloxacin with drugs has been reviewed. Ciprofloxacin reduces the area under the concentration-time curve of mycophenolate mofetil thus ciprofloxacin improves the elimination of mycophenolate mofetil [15], ciprofloxacin reduces the availability of diclofenac drops at ocular level [16], atorvastatin co-administered with ciprofloxacin leads to the formation of a charge-transfer complex which depletes the binding of these drugs to their respective receptors [17], the co-administration of ciprofloxacin with nonsteroidal anti-inflammatory drugs reduces the binding of GABA in brain causing an epileptogenic effect [18], ciprofloxacin inhibits the metabolism of caffeine, theophylline, and antipyrine [19], ciprofloxacin reduces the clearance of theophylline [20], ciprofloxacin increases the blood concentration of theophylline [21], probenecid reduces the renal elimination of ciprofloxacin by inhibiting the tubular secretion of ciprofloxacin [22], antacids containing magnesium and/or aluminium significantly reduce the absorption of ciprofloxacin [23]. These results indicate that ciprofloxacin interacts with drugs. The prophylaxis with ciprofloxacin has been reviewed in children. Ciprofloxacin reduces pneumonia, lung exacerbations, length of hospital stay, and mortality in high-risk children [24], reduces fever episodes in children with leukaemia and lymphoma [25], prevents multidrug-resistant infections which do not respond to standard antibiotic therapy in immunocompromised children [26], ciprofloxacin administered orally at a dose of 10 mg/kg thrice-daily prevents sepsis in malnourished children [27], and ciprofloxacin reduces the length of hospital stay in children with gam-negative bacteraemia [28]. These results indicate that the prophylaxis with ciprofloxacin prevents different infections in children. The treatment with ciprofloxacin has been reviewed in infants and children. Kaguelidou et al. [29] reviewed the literature relative to the treatment of bacterial infections with ciprofloxacin in infants. The treatment of infants with bacterial infection has been reported in three studies and the clinical response-rate ranges from 64% to 91% and no serious adverse-effects were observed. Fourteen studies indicated that ciprofloxacin treats bacterial infections and no serious adverse-effects were observed. Thirty infants with nosocomial infection caused by Pseudomonas aeruginosa were treated with ciprofloxacin intravenously at an initial dose of 10 mg/kg and the dose was increased to 40 mg/kg according to the clinical response. Two infants (6.6%) died and 28 infants (93.4%) were cured and no adverse-effects were observed. Ciprofloxacin administered orally at a dose of 15 mg/kg twice-daily for 10 days effectively treats infants with life-threatening infections caused by a multidrug-resistant Pseudomonas aeruginosa [30], ciprofloxacin administered orally at a dose of 20 mg/kg twice-daily for 10 days effectively treats children infected by Pseudomonas aeruginosa [31], ciprofloxacin administered intravenously at a dose of 20 mg/kg twice-daily for 10 days successfully treats children with dysentery and reduces the clinical and bacteriological signs and symptom of dysentery [32], a single oral dose of 500 mg of ciprofloxacin treats uncomplicated gonorrhoea in adolescents but causes irreversible cartilage toxicity [33], ciprofloxacin administered intramuscularly at a dose of 10 mg/kg twice-daily for 10 days effectively treats children with acute diarrhoea [34]. Children had typhoid fever caused by Salmonella typhi or by Salmonella paratyphi A and were treated with ciprofloxacin intravenously at a daily dose of 15 mg/kg for 10 days. This treatment is well-tolerated, effectively cures the children, and does not cause adverse-effects [35], and ciprofloxacin administered intravenously at a dose of 20 mg/kg twice-daily for 15 days treats shigellosis cholera and Escherichia coli gastroenteritis in children living in developing countries [36]. These results indicate that ciprofloxacin treats infants and children with different infections and causes few adverse-effects. The penetration of ciprofloxacin into the human cerebrospinal fluid has been reviewed. Ciprofloxacin was administered intravenously at a dose of 400 mg thrice-daily for 12 days to a patient with meningitis caused by Pseudomonas aeruginosa and the peak concentration of ciprofloxacin is 10.3 and 0.9 μg/ml in plasma and in the cerebrospinal fluid, respectively, and after one week of therapy the microorganism was eradicated from the cerebrospinal fluid [37]. Twenty-five patients had non-inflamed meninges (group A) and 9 patients had inflamed meninges (group B) and al patients received ciprofloxacin intravenously at a dose of 200 mg twice-daily for 10 days. In patients of group A the cerebrospinal fluid was sampled from 1 to 10 hours after the second dose of ciprofloxacin and the concentration of ciprofloxacin in the cerebrospinal fluid ranges from 0.073 to 0.106 μg/ml. In patients of group B the cerebrospinal fluid was sampled 5 times ranging from 1 to 9 hours after the second dose of ciprofloxacin and the concentration of ciprofloxacin in the cerebrospinal fluid ranges from 0.089 to 0.260 μg/ml. These results indicate that ciprofloxacin penetrates into the cerebrospinal fluid in concentration higher the MIC of Neisseria meningitis and gram-negative aerobic bacilli which are the bacteria causing the meningitis [38]. Nine patients with external ventriculostomy received ciprofloxacin intravenously at a dose of 200 mg twice-daily for 10 days and the elimination half-life of ciprofloxacin ranged from 260 to 430 min in the cerebrospinal fluid and from 145 to 170 min in serum. At 60 min after the dose the concentration of ciprofloxacin in the cerebrospinal fluid ranged from 0.042 to 0.223 μg/ml (median, 0.110) and this concentration is inadequate to treat bacterial infections in the central nervous system [39]. Twenty patients with purulent meningitis and 3 patients with ventriculitis received ciprofloxacin intravenously at a dose of 200 mg twice-daily for 14 days and the concentration of ciprofloxacin in the cerebrospinal fluid was measured on four occasions ranging from 60 to 480 min after dosing and ranged from 0.35 to 0.56 μg/ml. These concentrations are equal or higher the MICs of enterobacteria causing the meningitis or the ventriculitis [40]. These results indicate that ciprofloxacin penetrated into the cerebrospinal fluid in significant concentrations. The treatment of bacterial meningitis with ciprofloxacin has been reviewed in infants and children. Of 367 infants with meningitis caused by Escherichia coli, 86 infants (23.4%) presented neurologic complications, 201 infants (54.8%) received ciprofloxacin intravenously at a median daily dose of 30 mg/kg and 166 infants (45.2%) also received a third generation cephalosporin intravenously. Ciprofloxacin added to a third generation cephalosporin does not offer advantage for neurologic outcome and mortality in infants with meningitis caused by Escherichia coli [41], a preterm infant had the meningitis caused by Citrobacter koseri and received ciprofloxacin intravenously at a daily dose of 10 to 20 mg/kg plus cefotaxime administered intravenously at a daily dose of 100 mg/kg and this treatment lasted 21 days. Ciprofloxacin and cefotaxime should be considered the treatment of choice for treatment of meningitis caused by Citrobacter koseri [42], ciprofloxacin was administered intravenously at a daily dose of 10 to 60 mg/kg to 4 newborns and to 8 infants with meningitis. Six subjects (50%) had the meningitis caused by gram-negative bacteria and 6 subjects (50%) had the meningitis caused by gram-

positive bacteria. Ten subjects (83.3%) were cured and 2 subjects (16.7%) had reversible hydrocephalus which responded to treatment [43], twenty-eight preterm infants or low-birth-weight infants had the meningitis caused by Enterobacter cloacae and received ciprofloxacin intravenously at a daily dose of 4 to 40 mg/kg. The peak concentration of ciprofloxacin in the cerebrospinal fluid ranged from 0.10 to 1.45 μg/ml and this treatment cures the meningitis and does not cause adverse-effects [44], an infant had a meningitis caused by Salmonella paratyphi A resistant to ceftazidime and cefotaxime whereas this organism was eradicated with ciprofloxacin [45], five children had the meningitis caused by Klebsiella pneumoniae, Pseudomonas aeruginosa, or by Enterococcus faecium which were multidrug-resistant. Children received ciprofloxacin intravenously at a daily dose of 20 to 40 mg/kg for 14 to 21 days and this treatment eradicated these organisms from the cerebrospinal fluid [46], twenty young children had the meningitis caused by Salmonella typhimurium and received either ciprofloxacin intravenously or chloramphenicol, ampicillin, and clotrimazole intravenously. The cure-rate is 88.9% with ciprofloxacin and is 41.2% with chloramphenicol, ampicillin, and clotrimazole thus ciprofloxacin is the drug of choice for treatment of meningitis caused by Salmonella typhimurium [47], two children, aged 8 and 9 years, had the meningitis caused by Salmonella meningitidis resistant to imipenem, ceftriaxone, clotrimazole, and chloramphenicol whereas ciprofloxacin administered intravenously at a daily dose of 15 to 30 mg/kg treats the meningitis [48]. These results indicate that ciprofloxacin treats the meningitis caused by different bacteria. The transfer of ciprofloxacin across the human placenta has been studied using the placenta perfusion and ciprofloxacin is poorly transferred across the placenta [49]. The migration of ciprofloxacin into the breast-milk has been reported in two studies. Ten lactating women received 3 oral doses of 750 mg twice-daily of ciprofloxacin and the highest average concentration of ciprofloxacin in milk is 0.20 μg/ml and 12 to 24 hours after dosing the concentration of ciprofloxacin in milk is 0.20 and 0.02 μg/ml, respectively [50]. A lactating woman receive a single oral dose of 500 mg of ciprofloxacin and the concentration of ciprofloxacin in milk ranged from 6.0 to 9.1 μmol/L 4 times after dosing ranging from 4 to 16 hours [51]. These results indicate that ciprofloxacin poorly migrates into the breast-milk.

In conclusion, 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 for 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, Salmonella, Shigella, Enterobacter, Campylobacter, Chlamydia, Mycoplasma, Legionella, Brucella, Mycobacterium tuberculosis, Mycobacterium fortuitum, and Mycobacterium kansasii. Ciprofloxacin may be administered orally and intravenously and following oral administration is rapidly absorbed. Following oral administration, the absorption half-life of ciprofloxacin is 0.40 and 0.29 hours (P-value > 0.05) in infants and children, respectively, and the elimination half-life of ciprofloxacin is 2.73 and 1.28 hours, (P-value < 0.001) in infants and children, respectively. Ciprofloxacin is eliminated mainly by renal route and the renal function increases with infant maturation and children development thus the elimination half-life of ciprofloxacin is longer in infants. Ciprofloxacin has been found efficacy and safe in infants and children but can cause adverse-effects and the major adverse-effect is arthropathy which resolves with therapy. Ciprofloxacin interacts with drugs and the prophylaxis and treatment with ciprofloxacin have been reviewed. Ciprofloxacin penetrates into the cerebrospinal fluid in significant amounts and treats bacterial meningitis. Ciprofloxacin is poorly crossed across the human placenta and poorly penetrate into the breast-milk. The aim of this study is to review the clinical pharmacology of ciprofloxacin in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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References

1. MacDougall C. DNA Disruptors: Sulphonamides, Quinolones, and Nitroimidazoles. Brunton LL, Knollmann BC, editors. In: Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 14th Edition. Mc Graw Hill Education. 2023. Pp 1137-1146.
2. British National Formulary for Children from the British Medical Association, Royal Pharmaceutical Society, Royal College of Paediatricians and Child Health, Neonatal and Paediatric Pharmaceutics Group. 2022 – 2023. Pp 399-400.
3. Bonati M, Pandolfini C, Kaguelidou F, Kaguelidou F, Jacqz-Aigrain, E, Choonara I. Safety of ciprofloxacin in neonates with sepsis. Adv Drug React Bul. 2010; 265: 1019-1022.
4. Masoumi B, Eslami G, Alizadeh-Navaei R, Mondal P, Sadegh Rezai M. Safety Profile of Using Ciprofloxacin in Paediatrics: A Systematic Review and Meta-Analysis. Safety Profile of Using Ciprofloxacin in Paediatrics: A Systematic Review and Meta-Analysis. J Pediatr Rev 2019; 7: 129-140.
5. Heggers JP, Villarreal C, Edgar P, Wolf S, Klein GL, John SD, et al. Ciprofloxacin as a Therapeutic Modality in Pediatric Burn Wound Infections. Arch Surg. 1998; 133: 1247-1250.
6. Pradhan KM, Arora NK, Jena A, Susheela AK, Bhan MK. Safety of ciprofloxacin therapy in children: magnetic resonance images, body fluid levels of fluoride and linear growth. Acta Paediatr. 1995; 84: 555-560.
7. Kubin R. Safety and efficacy of ciprofloxacin in paediatric patients-review. Infection, 1993; 21: 413-421.
8. Chyský V, Kapila K, Hullmann R, Arcieri G, Schacht P, Echols R. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. Infection. 1991; 19: 289-296.
9. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011; 96: 874-880.
10. Burstein GR, Berman SM, Blumer JL, Moran JS. Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? Clin Infect Dis. 2002; 35: S191-S199.
11. Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011; 96: 874-800.
12. Zhao W, Hill H, Le Guellec C, Neal T, Mahoney S, Paulus S, et al. Population pharmacokinetics of ciprofloxacin in neonates and young infants less than three months of age. Antimicrob Agents Chemother. 2014; 58: 6572-6580.
13. Peltola H, Väärälä M, Renkonen OV, Neuvonen PJ. Pharmacokinetics of single-dose oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother. 1992; 36: 1086-1090.
14. Payen S, Serreau R, Munck A, Aujard Y, Aigrain Y, Bressolle, F, et al. Population pharmacokinetics of ciprofloxacin in pediatric

and adolescent patients with acute infections. Antimicrob Agents Chemother. 2003; 47: 3170-3178.
15. Goutelle S, Mialou V, Gouraud A, Parant F, Bleyzac N. Probable Drug Interaction Between Intravenous Ciprofloxacin and Mycophenolate Mofetil in a Bone Marrow Transplant Recipient. Pharmacotherapy. 2011; 31: 114-115.
16. Khan A, Iqbal1 Z, Khan MI, Khan JA, Khalid M, Javed M. Drug-drug interaction between ciprofloxacin and diclofenac ophthalmic drops at ocular level. Afr J Pharm Pharmacol. 2011; 5: 2566-2574.
17. Arayne MS, Sultana N, Bushra S, Rizvi S, Haroon U. In vitro drug interaction studies of atorvastatin with ciprofloxacin, gatifloxacin, and ofloxacin. Med Chem Res. 2010; 19: 717–731.
18. Janknegt R. Drug interactions with quinolones. J Antimicrob Chemother. 1990; 26: 7-29.
19. Davey PG. Overview of drug interactions with the quinolones. J Antimicrob Chemother. 1988; 22: 97-107.
20. Lode H. Drug Interactions with Quinolones. Rev Infect Dis. 1988; 10: S132-S136.
21. Davies BI, Maesen FP. Drug interactions with quinolones. Rev Infect Dis. 1989; 11: S1083-S1090.
22. Rubinstein E, Segev S. Drug interactions of ciprofloxacin with other non-antibiotic agents. Am J Med. 1987; 82: 119-123.
23. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med. 1989; 87: 76S-81S.
24. Onakpoya I, Onakpoya I, Hayward G, Heneghan C. Antibiotics for preventing lower respiratory tract infections in high-risk children aged 12 years and under. Cochrane Data Base Syst Rev. 2015; 9: CD011530.
25. Castagnola E, Moroni C, Bandettini R, Daniela D, Haupt R. Ciprofloxacin prophylaxis in children with acute leukemia in an era of increasing antibiotic resistance. Pediatr Infect Dis J. 2013; 32(5): 581.
26. Choi SH, Kim EY, Kim YJ. Systemic use of fluoroquinolone in children. Korean J Pediatr. 2013; 56: 196-201.
27. Thuo N, Ungphakorn W, Karisa J, Muchohi S, Muturi A, Kokwaro G, et al. Dosing regimens of oral ciprofloxacin for children with severe malnutrition: a population pharmacokinetic study with Monte Carlo simulation. J Antimicrob Chemother. 2011; 66: 2336-2345.
28. Yousef AA, Fryer CJH, Chedid FD, Abbas AAH, Felimban SK, Khattab T. A pilot study of prophylactic ciprofloxacin during delayed intensification in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2004; 43: 637-643.
29. Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates: a systematic review of the literature. Pediatr Infect Dis J. 2011; 30: e29-e37.
30. Belet N, Haciömeroğlu P, Küçüködük S. Ciprofloxacin treatment in newborns with multi-drug-resistant nosocomial Pseudomonas infections. Biol Neonate. 2004; 85: 263-268.
31. Connett GJ, Pike KC, Legg JP, Cathie K, Dewar A, Foote K, et al. Ciprofloxacin during upper respiratory tract infections to reduce Pseudomonas aeruginosa infection in paediatric cystic fibrosis: a pilot study. Ther Adv Respir Dis. 2015; 9: 272-280.
32. Traa BS, Walker CLF, Munos M, Black RE. Antibiotics for the treatment of dysentery in children. Int J Epidemiol. 2010; 39: 70-74.
33. Burstein GR, Berman SM, Blumer JL, Moran JS. Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? Clin Infect Dis. 2002; 35: S191-S199.
34. Leibovitz E, Janco J, Piglansky L, Press J, Yagupsky P, Reinhart H, et al. Oral ciprofloxacin vs. intramuscular ceftriaxone as empiric treatment of acute invasive diarrhea in children. Pediatr Infect Dis J. 2000; 19: 1060-1067.
35. Thomsen LL, Paerregaard A. Treatment with ciprofloxacin in children with typhoid fever. Scand J Infect Dis. 1998: 30: 355-357.
36. Green S, Tillotson G. Use of ciprofloxacin in developing countries. Pediatr Infect Dis J. 1997; 16: 150-159.
37. Lipman J, Allworth A, Wallis SC. Cerebrospinal fluid penetration of high doses of intravenous ciprofloxacin in meningitis. Clin Infect Dis. 2000; 31: 1131-1133.
38. Gogos CA, Maraziotis TG, Papadakis N, Beermann D, Siamplis DK, H, Bassaris HP. Penetration of ciprofloxacin into human cerebrospinal fluid in patients with inflamed and non-inflamed meninges. Eur J Clin Microbiol Infect Dis. 1991; 10: 511-514.
39. Nau R, Prange HW, Martell J, Sharifi S, Kolenda H, Bircher J. Penetration of ciprofloxacin into the cerebrospinal fluid of patients with uninflamed meninges. J Antimicrob Chemother. 1990; 25: 965-973.
40. Wolff M, Boutron L, Singlas E, Clair B, J Decazes M, Regnier B. Penetration of ciprofloxacin into cerebrospinal fluid of patients with bacterial meningitis. Antimicrob Agents Chemother 1987; 31: 899-902.
41. Tauzin M, Ouldali N, Lévy C, Béchet S, Cohen R, Caeymaex L. Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in Escherichia coli meningitis in infants: a multicentre propensity score-matched observational study. Clin Microbiol Infect. 2019; 25: 1006-1012.
42. McPherson C, Gal P, Ransom JL. Treatment of Citrobacter koseri infection with ciprofloxacin and cefotaxime in a preterm infant. Ann Pharmacother. 2008; 42: 1134-1138.
43. Krcméry V Jr, Filka J, Uher J, Kurak H, Sagát T, Tuharský J, et al. Ciprofloxacin in treatment of nosocomial meningitis in neonates and in infants: report of 12 cases and review. Diagn Microbiol Infect Dis. 1999; 35: 75-80.
44. van den Oever HL, Versteegh FG, Thewessen EA, van den Anker JN, Mouton JW, Neijens HJ. Ciprofloxacin in preterm neonates: case report and review of the literature. Eur J Pediatr. 1998; 157: 843-845.
45. Bhutta ZA, Farooqui BJ, Sturm AW. Eradication of a multiple drug resistant Salmonella paratyphi A causing meningitis with ciprofloxacin. J Infect. 1992; 25: 215-219.
46. Karaaslan A, Kadayifçi EK, Turel O, Toprak DG, Soysal A, Bakir M. Intraventricular ciprofloxacin usage in treatment of multidrug-resistant central nervous system infections: report of four cases. Pediatr Rep. 2014; 6(3): 5619.
47. Owusu-Ofori A, Scheld WM. Treatment of Salmonella meningitis: two case reports and a review of the literature. Int J Infect Dis. 2003; 7: 53-60.
48. Price EH, de Louvois J, Workman MR. Antibiotics for Salmonella meningitis in children. J Antimicrob Chemother. 2000; 46: 653-655.
49. Polachek H, Holcberg G, Sapir G, Tsadkin-Tamir M, Polachek JP, Katz M, et al. Transfer of ciprofloxacin, ofloxacin and levofloxacin across the perfused human placenta in vitro. Eur J Obstet Gynecol Reprod Biol. 2005; 122: 61-65.
50. Kaplan YC, Koren G. Use of ciprofloxacin during breastfeeding. Can Fam Physician. 2015; 61: 343-344.
51. Cover DL, Mueller BA. Ciprofloxacin penetration into human breast milk: a case report. DICP. 1990; 24: 703-704.

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