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Research Article

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Clinical pharmacology of fluoroquinolones in infants and children

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Abstract

The fluoroquinolones used in paediatric patients are: ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin. The fluoroquinolones are potent bactericidal agents against Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter, and Campylobacter. The activity against streptococci is significantly greater with newer agents including levofloxacin, gemifloxacin, and moxifloxacin. Several intracellular bacteria are inhibited by fluoroquinolones that can be achieved in plasma; these include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium (including Mycobacterium tuberculosis). Most fluoroquinolones are well absorbed after an oral dose and the peak plasma concentrations of fluoroquinolones are obtained within 1 to 3 hours after an oral dose. The mean use of ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin is the treatment of eye infections. The mean elimination half-life of ciprofloxacin is 2.73 hours in newborns and 1.28 hours in children (P-value < 0.001). The elimination half-life of levofloxacin increases with the child age and ranges from 2.46 to 5.45 hours. The mean elimination half-life moxifloxacin and ofloxacin is 4.14 and 3.49 hours, respectively. The transfer of fluoroquinolones across the human placenta has been reported for ciprofloxacin, levofloxacin, and ofloxacin and these fluoroquinolones are poorly transferred across the human placenta. The migration of fluoroquinolones into the breast-milk has been reported for ciprofloxacin, levofloxacin, and ofloxacin and these fluoroquinolones poorly migrate into the breast-milk. The aim of this study is to review the dosing, pharmacokinetics, treatment, placental transfer, and migration into the breast-milk of ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin.

Keywords: breast-milk, ciprofloxacin, dosing, drug interaction, efficacy-safety, levofloxacin, moxifloxacin, ofloxacin, pharmacokinetics, placental transfer, and treatment.

Introduction

The fluoroquinolones used in paediatric patients are: ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin.

Mechanism of Action. Dosing. and use of Fluoroquinolones

The fluoroquinolone antibiotics target bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria, topoisomerase IV is the primary target. In contrast, DNA gyrase is the primary fluoroquinolone target in many gram-negative bacteria. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling that can occur during DNA replication. The fluoroquinolones inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth (0.1 to 10 µg/ml). Mutations of the gene that encodes the A subunit of the gyrase can confer resistance to these drugs. Topoisomerase IV which separates interlinked (concatenated) daughter DNA molecules are the product of DNA replication. Eukaryotic cells do not contain DNA gyrase. They do contain a conceptually and mechanistically similar type II DNA topoisomerase, but fluoroquinolones inhibit it only at concentrations (100 to 1,000 µg/ml) much higher than those needed to inhibit the bacterial enzymes. The fluoroquinolones are potent bactericidal agents against Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter, and Campylobacter. Some fluoroquinolones are active against Pseudomonas species, with ciprofloxacin and levofloxacin having substantial enough activity for use in systemic infections. Fluoroquinolones have good activity in-vitro 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 newer agents, including levofloxacin, gemifloxacin, and moxifloxacin. Several intracellular bacteria are inhibited by fluoroquinolones that can be achieved in plasma; these include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium (including Mycobacterium tuberculosis). Ciprofloxacin, ofloxacin, and moxifloxacin have MIC90 values from 0.5 to 3 µg/ml, for Mycobacterium fortuitum, Mycobacterium kansasii, and Mycobacterium tuberculosis. Moxifloxacin also has useful activity against anaerobes. Most fluoroquinolones are well absorbed after oral administration. Peak plasma concentrations of fluoroquinolones are obtained within 1 to 3 hours af-

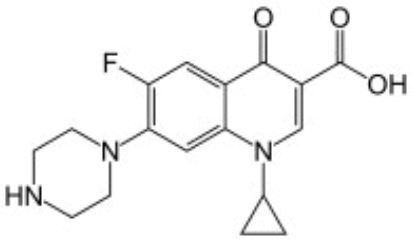
ter an oral dose. The distribution volume of fluoroquinolones is high, with concentrations in urine, kidney, lung, and prostate tissue, stool, bile, macrophages, and neutrophils higher than serum concentrations. Except for moxifloxacin, quinolones are cleared predominantly by the kidney, and dosages must be adjusted for renal failure. Moxifloxacin should not be used in patients with hepatic failure [1].

Literature search

The literature search was performed electronically using PubMed database as search engines. The following key words were used: "Ciprofloxacin children", "levofloxacin children", "moxifloxacin children", and "ofloxacin children". In addition the book: "Pharmacological Basis of Therapeutics [1] has been consulted.

Results

Ciprofloxacin



Ciprofloxacin molecular structure (molecular weight = 331.346 grams/mole)

Administration schedule of ciprofloxacin to children [2]

Administration of ciprofloxacin to treat superficial bacteria eye infection (using the eye drop)

Administration to children

Children. Apply 4 times-daily for maximum duration of 21 days.

Administration of ciprofloxacin to treat superficial bacteria eye infection (using the eye ointment)

Administration to children

Children. Apply 1.25 centimetres thrice-daily for 2 days, and then apply 1.25 centimetres twice-daily for 5 days.

Administration of ciprofloxacin to treat superficial bacterial eye severe infection (using the eye drop)

Administration to children

Children. Apply twice-daily during waking hours for 2 days, and then apply 4 times-daily for a maximum duration of 21 days.

Administration of ciprofloxacin to treat corneal ulcer (using eye drop)

Administration to children

Children. Apply every 15 min for 6 hours, and then apply every 30 min for the remainder of 1 day, and then apply 6 times-daily on days 3 to 14, for a maximum duration of 21 days, to be administered thought the day and night.

Administration of ciprofloxacin to treat corneal ulcer (using eye ointment)

Administration to children

Children. Apply 1.25 centimetres every 1 or 2 days for 2 days, and then apply 1.25 centimetres 6 times-daily for the next 12 days, to be administered throughout the day and night.

Efficacy and safety of ciprofloxacin

Ciprofloxacin is an efficacy and safe therapeutic option for newborns with sepsis caused by multidrug-resistant bacteria [3]. Ciprofloxacin was administrated to newborns as a salvage therapy for sepsis due to multidrug-resistant strains and ciprofloxacin was found to be efficacy and safe and treated the sepsis [4]. One-thousand-five-hundred paediatric patients who were suffering from acute infections or for bronchopulmonary exacerbations due to Pseudomonas aeruginosa were treated with ciprofloxacin which effectively and safety treated these infections [5]. Musculoskeletal adverse-effects are caused by ciprofloxacin in paediatric patients however these musculoskeletal events are reversible indicating that ciprofloxacin is safe in these patients [6].

Pharmacokinetics of ciprofloxacin in infants and children

Peltola et al. [7] studied the pharmacokinetics of ciprofloxacin in 7 newborns, aged 5 to 10 weeks, and in 8 children, aged 12 months to 5 years, and a single oral dose of 15 mg/kg of ciprofloxacin was administered to these newborns and children.

Table 1: Pharmacokinetic parameters of ciprofloxacin which have been obtained in 7 newborns and in 8 children following a single oral dose of 15 mg/kg of ciprofloxacin. Values are the minimum, maximum, mead, and ±SD, by Peltola et al. [7].

Value	Peak conc. (µg/ml)	Tmax (h)	$T_{1/2}$ absorption (h)	$T_{1/2}$ (h)	AUC (µg*h/ml)	MRT (h)
Newborns						
Minimum	1.4	0.62	0.10	2.40	7.1	3.7
Maximum	5.0	2.00	0.74	3.20	28.2	5.8
Mean	3.3	1.18	0.40	2.73	16.1	4.6
±SD	1.3	0.46	0.22	0.28	7.4	0.8
Children						
Value	**Peak conc. (µg/ml)**	**Tmax (h)**	**$T_{1/2}$ absorption (h)**	**$T_{1/2}$ (h)**	**AUC (µg*h/ml)**	**MRT (h)**
Minimum	0.50	0.50	0.17	0.64	0.9	1.5
Maximum	5.3	1.50	0.59	2.10	9.2	3.3
Mean	2.1	1.00	0.29	1.28	5.3	2.4
±SD	1.7	0.25	0.16	0.52	3.3	0.60
*P-value	> 0.05	> 0.05	> 0.05	< 0.001	< 0.01	< 0.001

Tmax = time to reach the peak concentration. $T_{1/2}$ absorption = absorption half-life. $T_{1/2}$ = elimination half-life. AUC = area under the concentration-time curve. MRT = mean residence time. *Student t test for unpaired data.

This table shows that ciprofloxacin is rapidly absorbed following oral administration as the mean time to reach the peak concentration is about 1 hour, the mean absorption half-life ranges from 0.29 to 0.40 hours, and ciprofloxacin is rapidly eliminated. The mean elimination half-life is longer in newborns than in children, the area under the concentration-time curve is higher in newborns, and the mean residence time is higher in newborns than in children. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the wide variation of subject age and disease.

Treatment of bacterial infections with ciprofloxacin

Ciprofloxacin effectively treats the infant meningitis caused by Citrobacter koseri [8]. Ciprofloxacin effectively treats life-threatening infections caused by multidrug-resistant Pseudomonas aeruginosa in newborns [9]. Ciprofloxacin effectively treats neonatal infection caused by multidrug-resistant gram-negative organisms [10]. Ciprofloxacin effectively treats neonatal infection caused by multidrug-resistant gram-negative organisms [11]. Ciprofloxacin effectively treats infections in preterm and term infants caused by bacteria which are resistant to other antibiotics [12]. An oral ciprofloxacin dose of 10 mg/kg given thrice-daily is an alternative antibiotic for the management of sepsis in severely malnourished children [13].

Interaction of ciprofloxacin with dugs

Co-administration of ciprofloxacin with theophylline is associated with a significant increase risk of theophylline toxicity [14]. Ciprofloxacin increases the serum concentration of theophylline by 60% [15]. Ciprofloxacin interacts with cytochrome P450 and suppresses cytochrome P450 at the transcriptional level [16]. Ciprofloxacin increased the caffeine elimination half-life [17].

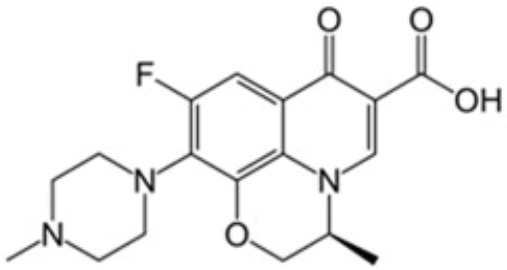
Transfer of ciprofloxacin across the human placenta

Ciprofloxacin was administered to 5 pregnant women at term of pregnancy. Ciprofloxacin crosses the placenta; its mean concentration in the fetal compartment is 0.3 µg/ml, accounting for 22% of the maternal concentration after 3 hours. The fetal to maternal ciprofloxacin concentration ratio is 0.53 [18]. The transfer of ciprofloxacin across the human placenta was studied using the placenta perfusion and only a small fraction of ciprofloxacin passes from the maternal to the fetal compartment [19].

Migration of ciprofloxacin into the breast-milk

Ten lactating women received ciprofloxacin orally at a dose of 750 mg twice-daily for 3 doses. Milk ciprofloxacin concentration was measured after the third dose. The highest milk concentration of ciprofloxacin averaged to 3.79 µg/ml which occurred 2 hours after the dose. Average milk concentration then fell as follows: 2.26 µg/ml at 4 hours, 0.86 µg/ml at 6 hours, 0.51 µg/ml at 9 hours, 0.2 µg/ml at 12 hours, and 0.02 µg/ml at 24 hours after the dose [20]. These results indicate that ciprofloxacin poorly migrates into the breast-milk.

Levofloxacin



Levofloxacin molecular structure (molecular weight = 361.368 grams/mole)

Administration schedule of levofloxacin to children [21]
Administration of levofloxacin to treat eye infections

Administration to children

Children. Apply every 2 to 4 hours for the first 2 days, and then reduce the dosing to 4 times-daily for a maximum of 10 days of treatment (using the eye drop).

Efficacy and safety of levofloxacin

Levofloxacin is safe and efficacy in treatment of late-onset sepsis in premature infants [22]. Levofloxacin is safe and effective in preventing tuberculosis disease in young children who have been exposed to multidrug-resistant tuberculosis [23]. Levofloxacin is well-tolerated and effective for the treatment of community-acquired pneumonia in infants and children [24]. Levofloxacin is safe and efficacy as amoxicillin/clavulanate for the treatment of recurrent and/or persistent acute otitis media in infants and children [25].

Pharmacokinetics of levofloxacin in children

Mase et al. [26] studied the pharmacokinetics of levofloxacin in 50 children, aged 0.5 to 15 years (median, 8 years) who received levofloxacin orally at a dose of 25 mg/kg once-daily. Table 2 summarizes the characteristics of children included in the study and table 3 provides the pharmacokinetic parameters of levofloxacin.

Table 2: Characteristics of children included in the study. Federal states of Micronesia (FSM) and Republic of the Marshall Islands (RMI). Values are the mean±SD, by Mase et al. [26].

	FSM (N = 33)	RMI (N = 17)	Total (N = 50)
Characteristics			
Age (years)	8.5±3.7	11.0±4.8	9.3±4.2
≤ 5, N (%)	10 (30)	3 (18)	13 (26)
5 to 11, N (%)	12 (36)	4 (24)	16 (32)
11 to 17, N (%)	11 (34)	10 (59)	21 (42)
Body-weight (kg)	26.2±9.2	34.9±17.2	29.2±13.1
Body height (meter)	1.18±0.20	1.31±0.28	1.23±0.24
Boys, N (%)	17 (52)	9 (53)	26 (52)
Girls, N (%)	16 (49)	8 (47)	24 (49)
Food intake 1 to 3 hours before, N (%)			
Yes	29 (91)	12 (71)	41 (84)
No	3 (9)	5 (29)	8 (16)
Participant status, N (%)			
Case	8 (24)	0 (0)	8 (16)
Contact	25 (75)	17 (100)	42 (84)
Drug regimen, N (%)			
Levofloxacin	17 (52)	0 (0)	17 (35)
Levofloxacin/Ethambutol	8 (24)	17 (100)	32 (65)
Multidrug-resistant regimen	8 (24)	0 (0)	8 (24)

Table 3: Pharmacokinetic parameters of levofloxacin which have been obtained in 50 children who received levofloxacin orally at a dose of 25 mg/kg once-daily. Values are the mean±SD, by Mase et al. [26].

Age (years)	N	Ka (h-1)	DV/F (L/kg)	TBC/F (L/h/kg)	$T_{1/2}$ (h)	Peak conc. (µg/ml)	Tmax (h)	AUC0-6h (µg*h/ml)
0.5 - < 2	3	0.39±0.31	0.74±0.46	0.26±0.15	2.46±1.38	13.54±3.058	1±0.0	52.47±23.0
2 - < 5	7	0.19±0.05	1.24±0.43	0.24±0.11	3.83±1.12	10.58±3.62	1.14±0.38	44.79±15.0
5 - < 10	18	0.18±0.07	1.49±0.73	0.23±0.07	4.89±3.08	6.77±2.69	1.44±0.51	28.10±10.1
10 - < 12	5	0.18±0.05	1.3±0.30	025±0.17	4.03±0.89	6.95±1.97	1.20±0.45	29.37±9.20
12 - < 17	17	0.14±0.05	1.38±0.44	0.18±0.06	5.45±1069	7.41±2.17	1.31±0.49	32.17±10.10

Ka = absorption-rate constant. DV = distribution volume. TBC = total body clearance. $T_{1/2}$ = elimination half-life. Tmax = time to reach the peak concentration. AUC = area under the concertation-time curve.

This table shows that the absorption-rate constant is higher in younger children, the distribution volume is lower in younger children, the elimination half-life increases with the child age, the peak concentration is higher in younger children, and the area under the concentration-time curve is higher in younger children. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the wide variation of child age and disease.

Treatment of bacterial infections with levofloxacin

Levofloxacin was administered orally at a dose of 10 mg/kg twice-daily to 6 newborns, with a postmenstrual age of 26 to 42 weeks, to treat multidrug-resistant nosocomial respiratory-tract infections and this treatment effectively managed the infections in these newborns [27]. Levofloxacin was safe and effective in eradicating common bacterial pathogens from middle ear fluid in children with, or at risk for, of recurrent or persistent otitis media [28].

Interaction of levofloxacin with drugs

Combinations of levofloxacin with β-lactams or amikacin enhanced the activity against Pseudomonas aeruginosa and Acinetobacter species [29]. Co-administration of levofloxacin with clarithromycin inhibited theophylline metabolic pathways catalysed by both CYP1A2 and CYP3A4 and resulted in the decrease of theophylline clearance [30]. Levofloxacin prolonged the prothrombin response in patients undergoing chronic warfarin therapy [31].

Transfer of levofloxacin across the human placenta

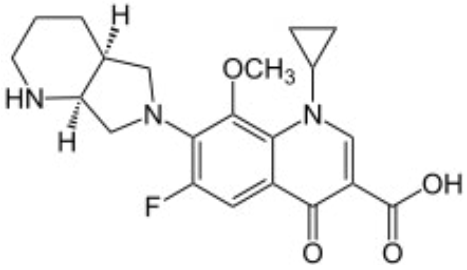
The transfer of levofloxacin across the human placenta was studied using the placenta perfusion and only a small fraction of levofloxacin passed from the maternal to the fetal compartment [19].

Migration of levofloxacin into the breast-milk

One woman received levofloxacin intramuscularly at a dose of

500 mg daily for 9 days, then orally for 17 days. Twenty-six milk samples were obtained after 10 days of therapy and continued for 6 days after discontinuation of therapy. The peak concentration of levofloxacin in the milk was 8.2 µg/ml at 5 hours after the dose. The milk concentrations fell with a half-life of 7 hours and traces of levofloxacin in the milk were detectable 65 hours after the dose [32]. These results indicate that levofloxacin poorly migrates into the breast-milk.

Moxifloxacin



Moxifloxacin molecular structure (molecular weight = 401,431)"
under the molecular structure of moxifloxacin.
Administration schedule of moxifloxacin to children [33]
Administration of moxifloxacin to treat eye infections

Administration to children

Children. Apply trice-daily and continue the treatment for 2 to 3 days after the infection improves; repeat the treatment if no improvement is reached within 5 days (using the eye drop).

Pharmacokinetics of moxifloxacin in children

Thee et al. [34] studied the pharmacokinetics of moxifloxacin in 23 children, aged 7 to 15 years, with multidrug-resistant tuberculosis and HIV who received moxifloxacin orally at a dose of 7.5 or 10 mg/kg once-daily. Table 4 summarizes the demographic and clinical characteristics of children included in the study and table 5 provides the pharmacokinetic parameters of moxifloxacin

Table 4: Demographic and clinical characteristics of the children included in the study. Values are the number and (%), by Thee et al. [34].

Characteristic	Number and (%)
Male sex	9 (39.1)
Black	13 (56.5)
Mixed ethnicity	10 (43.5)
Previous tuberculosis episodes or treatment	11 (47.8)
Known current tuberculosis source case	12 (52.2)
Certainty of tuberculosis diagnosis	
Bacteriologically confirmed	20 (87.0)
Probable tuberculosis	3 (13.0)
Tuberculosis disease type	
Pulmonary tuberculosis	14 (60.9)
Extra-pulmonary tuberculosis	3 (13.0)
Pulmonary tuberculosis and extra-pulmonary tuberculosis	6 (26.1)
HIV-infected	6 (26.1)
Weight-for-age z score < 2.0	3 (13.0)

Table 5: Pharmacokinetic parameters of moxifloxacin which have been obtained in 23 children with multidrug-resistant tuberculosis and HIV who received moxifloxacin orally at a dose of 7.5 or 10 mg/kg once-daily. Values are the median and the (interquartile range), by Thee et al. [34].

Parameter	Number of children	Moxifloxacin
Peak conc. (µg/ml)	23	3.08 (2.85 – 3.82)
Tmax (h)	23	2.0 (1.0 – 8.0)
TBC/F (L/h)	12	10.53 (7.23 – 14.14)
DV (L)	12	70.61 (57.53 – 77.70)
C_0 (µg/ml)	12	4.14 (3.38 – 4.86)
$T_{1/2}$ (h)	12	4.14 (3.45 – 6.11)
$AUC_{0\text{-}8h}$ (µg*h/ml)	23	17.24 (14.47 – 21.99)
$AUC_{0\text{-}24h}$ (µg*h/ml)	12	23.31 (19.24 – 42.30)

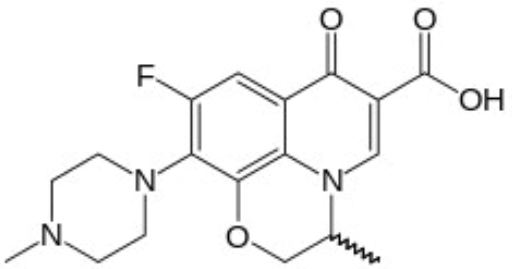
Tmax = time to reach the peak concentration. TBC = total body clearance. DV = distribution volume, C_0 = concentration at time 0. $T_{1/2}$ = elimination half-life. AUC = area under the concentration-time curve.

This table shows that moxifloxacin is rapidly absorbed after oral administration as the mean time to reach the peak concentration is 2 hours, the distribution volume is larger than the water volume, and moxifloxacin is slowly eliminated as the mean elimination half-life is 4.14 hours. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by a wide variation of the child age and disease.

Treatment of bacterial infections with moxifloxacin

Moxifloxacin was administered orally to 10 children with mycobacterial diseases and moxifloxacin effectively treated the infection in all children [35]. Moxifloxacin treatment was well tolerated and effectively treated children with complicated intraabdominal infections [36]. Moxifloxacin 0.5% eye drops provided a more and rapid effective clinical cure than tobramycin 0.3% eye drops in the treatment of purulent conjunctivitis in children [37]. Adverse-effects that occur during paediatric moxifloxacin therapy are relatively common but rarely serious enough to require premature discontinuation and the drug may be used safely in most children [38].

Ofloxacin



Ofloxacin molecular structure (molecular weight = 361.368 grams/mole)

Administration schedule of ofloxacin to children [39]

Administration of ofloxacin to treat eye infections

Administration to children

Children. Apply every 2 to 4 hours for the first 2 days, and then reduce the dose to 4 times-daily for a maximum of 10 days of treatment (using the eye drop).

Pharmacokinetics of ofloxacin in children

Garcia-Prats et al. [40] studied the pharmacokinetics of ofloxacin in 85 children with tuberculosis, aged 1.9 to 15 years (median, 3.4), and ofloxacin was administered orally at a dose of 20 mg/kg once-daily. Table 6 summarizes the characteristics of children included in the study and able 7 provides the pharmacokinetic parameters of ofloxacin.

Table 6: Demographic and clinical characteristics of children included in the study. Values are the number and (%), by Garcia-Prats et al. [40].

Characterises	N (%) children with MDR-TB disease (N = 55)	N (%) children receiving MDR-TB preventive therapy (N = 30)
Age (years)		
0 to < 2	16 (29.1)	8 (26.7)
2 to < 5	17 (30.9)	22 (73.3)
5 to < 15	22 (58.2)	0 (0.00)
Male sex	32 (58.2)	15 (50.0)
Certainty of tuberculosis	20 (36.4)	---
Probable tuberculosis	30 (58.2)	---
Suspected tuberculosis	3 (5.5)	---
Tuberculosis disease type		
Pulmonary tuberculosis only	40 (72.7)	---
Extra-pulmonary tuberculosis only	5 (9.1)	---
Pulmonary and extra-pulmonary tuberculosis	10 (18.2)	---
HIV infected	11 (20)	0 (0.00)

MDR-TB = multidrug-resistant tuberculosis.

Table 7: Pharmacokinetic parameters of ofloxacin which have been obtained in 85 children with tuberculosis, aged 1.9 to 15 years (median, 3.4), and ofloxacin was administered orally at a dose of 20 mg/kg once-daily. Values are the mean (range) except for Tmax, TBC/F, and DV which are presented as the median (range), by Garcia-Prats et al. [40].

Parameter	N	Value
Peak conc. (µg/ml)	85	8.97 (2.47 – 14.4)
Tmax (h)	85	2.0 (1.0 – 4.0)
Elimination half-life (h)	72	3.49 (1.89 – 6.95)
TBC/F (L/h/kg)	72	0.31 (0.11 – 1.06)
Distribution volume (L/kg)	72	1.45 (0.86 – 6.49)
$AUC_{0\text{-}8h}$ (µg*h/ml)	85	44.2 (12.1 – 75.8)
$AUC_{0\text{-}24h}$ (µg*h/ml)	72	66.7 (18.8 – 121)

Tmax = time to reach the peak concentration. TBC = total body clearance. AUC = area under the concentration-time curve.

This table shows that ofloxacin is rapidly absorbed after oral dosing as the mean Tmax is 2.0 hours, ofloxacin is slowly eliminated as the mean elimination half-life is 3.49 hours and the distribution volume of ofloxacin is similar to the water volume. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the wide variation of child age and disease.

Treatment of bacterial infections with ofloxacin

Ofloxacin eardrops managed chronic suppurative otitis media in children [41]. Otic ofloxacin drops prevented infections in children undergoing tympanosotomy tube plugging and treated otorrhea [19]. In the treatment of otitis externa in children, once-daily ofloxacin otic solution was effective and safe as neomycin sulfate/polymyxin B sulfate/hydrocortisone otic suspension given four times-daily [42]. Ofloxacin applied topically to children with tympanosotomy tubes placement and purulent otorrhea is efficacious as oral amoxicillin/clavulanate [43].

Transfer of ofloxacin across the human placenta

The transfer of ofloxacin across the human placenta was studied using the placenta perfusion and only a small fraction of ofloxacin passed from the maternal to the fetal compartment [19].

Migration of ofloxacin into the breast-milk

Ten lactating women received ofloxacin orally at a dose of 400 mg twice-daily for 3 doses and the milk concentration of ofloxacin was measured after the third dose. The highest concentration of ofloxacin averaged to 2.41 µg/ml which occurred 2 hours after the dose. Average milk concentration then fell as follows: 1.91 µg/ml at 4 hours, 1.25 µg/ml at 6 hours, 0.64 µg/ml at 9 hours, 0.29 µg/ml at 12 hours, and 0.05 µg/ml at 24 hours after the dose. These results indicate that ofloxacin poorly migrates into the breast-milk [20].

Discussion

The fluoroquinolones used in paediatric patients are: ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin. The fluoroquinolone antibiotics target bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria, topoisomerases IV is the primary target. In contrast, DNA gyrase is the primary fluoroquinolone target in many gram-negative bacteria. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling that can occur during DNA replication. The fluoroquinolones inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth (0.1 to 10 µg/ml). The fluoroquinolones are potent bactericidal agents against Proteus, Escherichia coli, Klebsiella, and various species of Salmonella, Shigella, Enterobacter, and Campylobacter. The activity against streptococci is significantly greater with newer agents, including levofloxacin, gemifloxacin, and moxifloxacin. Several intracellular bacteria are inhibited by fluoroquinolones that can be achieved in plasma; these include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium (including Mycobacterium tuberculosis). Ciprofloxacin, ofloxacin, and moxifloxacin have MIC90 values from 0.5 to 3 µg/ml for Mycobacterium fortuitum, Mycobacterium kansasii, and Mycobacterium tuberculosis. Most fluoroquinolones are well absorbed after an oral dose and the peak plasma concentrations of fluoroquinolones are obtained within 1 to 3 hours after an oral dose. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are mainly used to treat eye infection. Ciprofloxacin may be applied as an ointment or as eye drop whereas levofloxacin, moxifloxacin, and ofloxacin are applied as eye drop [1]. The efficacy and safety of ciprofloxacin have been reported [3-6] and the pharmacokinetics of ciprofloxacin have been studied in newborns and children and the mean elimination half-life of ciprofloxacin is 2.73 and 1.28 hours in newborns and children, respectively (P-value < 0.001) [7]. The treatment of bacterial infections with ciprofloxacin has been reported [8-13] and ciprofloxacin interacts with drugs [14-17]. Ciprofloxacin increases the serum concentration of theophylline [14, 15] and increase the risk of theophylline toxicity [14]. Ciprofloxacin interacts with cytochrome P450 and suppresses cytochrome P450 at the transcriptional level [16], and ciprofloxacin increases the caffeine elimination half-life [17]. The transfer of ciprofloxacin across the human placenta was studied in-vivo [18] and in-vitro [19], ciprofloxacin is poorly transferred across the human placenta, and ciprofloxacin poorly migrates into the barest-milk [20]. Levofloxacin has been found efficacy and safe in infants and children [22-25] and the pharmacokinetics of levofloxacin have been studied in children aged 0.5 to 15 years [26]. The mean elimination half-life of levofloxacin ranged from 2.46 to 5.45 hours being shorter in younger than older children. The treatment of bacterial infections with levofloxacin has been studied in newborns [27] and children [28] and levofloxacin interacts with drugs [29-31]. The combinations of levofloxacin with β-lactams or with amikacin enhance the activity against

Pseudomonas aeruginosa and Acinetobacter species [29]. The co-admiration of levofloxacin with clarithromycin inhibits the theophylline metabolic pathways catalysed by both CYP1A2 and CYP3A4 and results in decrease of theophylline clearance [30] and levofloxacin prolongs the prothrombin response in patients undergoing chronic warfarin therapy [31]. Levofloxacin is poorly transferred across the human placenta [19] and poorly migrates into the breast-milk [32]. The pharmacokinetics of moxifloxacin have been studied in children and the median elimination half-life is 4.14 hours [34] and moxifloxacin treats bacterial infections [35-38]. The pharmacokinetics of ofloxacin have been studied in children aged 1.9 to 15 years (median, 3.4) and the mean elimination half-life is 3.49 hours [40]. The treatment of bacterial infections with ofloxacin has been reported [41-43], ofloxacin is poorly transferred across the human placenta [19], and poorly migrates into the breast-milk [20].

In conclusion, the fluoroquinolones used in paediatric patients are: ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin. Ciprofloxacin has been found efficacy and safe in newborns and children and the mean elimination half-life of ciprofloxacin is 2.73 and 1.28 hours in newborns and children, respectively (P-value < 0.001). The treatment of bacterial infections with ciprofloxacin has been reported, ciprofloxacin interacts with drugs, ciprofloxacin is poorly transferred across the human placenta, and poorly migrates into the breast-milk. Levofloxacin has been found efficacy and safe in infants and children and the pharmacokinetics of levofloxacin have been studied in children aged 0.5 to 15 years and the mean elimination half-life ranges from 2.46 to 5.45 hours being shorter in younger than older children. The treatment of bacterial infections with levofloxacin has been reported, levofloxacin interacts with drugs, levofloxacin is poorly transferred across the human placenta, and poorly migrates into the breast-milk. The pharmacokinetics of moxifloxacin have been studied in children, the median elimination half-life is 4.14 hours, and moxifloxacin treats bacterial infections. The pharmacokinetics of ofloxacin have been studied in children aged 1.9 to 15 years (median, 3.4), the median elimination half-life is 3.49 hours, ofloxacin treats bacterial infections, is poorly transferred across the human placenta and poorly migrates into the breast-milk.

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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