SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Review Article

Clinical Pharmacology of Cefotaxime in Infants and Children

Gian Maria Pacifici*

Department of Pharmacology, University of Pisa, Italy

***Corresponding author**
Gian Maria Pacifici, Department of Pharmacology, University of Pisa, Associate professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy, Email: pacifici44@tiscali.it

Submitted: 29 April 2021

Accepted: 26 May 2021

Published: 29 May 2021

ISSN: 2333-7079

Keywords
- Cefotaxime
- Desacetylcefotaxime
- Dosing
- Metabolism
- Pharmacokinetics
- Treatment
- Meningitis
- Breast-milk
- Infants
- Children

Abstract

Cefotaxime is active against Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus and Streptococcus pneumoniae. Cefotaxime cured the meningitis caused by Haemophilus influenzae, penicillin-sensitive Streptococcus pneumoniae, and Neisseria meningitides. The drug is metabolized in-vivo to desacetylcefotaxime and desacetylcefotaxime is converted into 3-desacetylcefotaxime lactone. Cefotaxime is administered intravenously and the dose is 50 mg/kg given twice-daily, thrice-daily, and 4 times-daily in infants with a postnatal age of 1 week, 2 to 3 weeks and > 3 weeks, respectively, and it is 50 mg/kg thrice-daily in children. The elimination half-life of cefotaxime ranges from 3 to 5 hours in infants and it is about 0.8 hours in children. The total body clearance of cefotaxime ranges from 0.1 to 0.3 L/h/kg in infants, it is 0.11 and 0.74 L/h/kg in two children, and the renal clearance is lower than the total body clearance. The total body clearance of desacetylcefotaxime is about 0.36 L/h/kg. Cefotaxime distribution volume is lower than the water volume in both infants and children. This drug interacts with drugs; the interaction may cause inhibitory or synergistic effects and the treatment with cefotaxime has been extensively studied in infants and children. Cefotaxime penetrates into the cerebrospinal fluid and the cerebrospinal fluid to serum ratio ranges from 10 to 26% for cefotaxime and from 21 to 29% for desacetylcefotaxime. Cefotaxime is transferred across the human placenta and the umbilical cord to maternal blood ratio is 77% for cefotaxime and 99% for desacetylcefotaxime. Cefotaxime migrates into the breast-milk in significant amounts. The aim of this study is to review the dosing, efficacy and safety, metabolism, pharmacokinetics, drug-interactions, treatment, meningitis, penetration into the cerebrospinal of cefotaxime in infants and children, and cefotaxime transfer across the human placenta and migration into the breast-milk.

INTRODUCTION

Cefotaxime is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. However, activity against Bacillus fragilis is poor, and the increasingly prevalent ESBLs and KPCs confer resistant to cefotaxime. Cefotaxime has a half-life in plasma of about 1 hour in adults and should be administered thrice-daily to 6 times-daily for serious infections. The drug is metabolized in-vivo to desacetylcefotaxime, which is less active than is the parent drug. Concentrations achieved in the cerebrospinal fluid are adequate for treatment of meningitis caused by Haemophilus influenzae, penicillin-sensitive Streptococcus pneumoniae, and Neisseria meningitides [1].

Spectrum of activity of cefotaxime

Cefotaxime is active against Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, and Streptococcus pyogenes [1].

Therapeutic use of cefotaxime

The third-generation of cephalosporins, thus cefotaxime, are the drug of choice for serious infections caused by Escherichia coli, Klebsiella, Proteus, Providencia, Serratia, and Haemophilus influenzae. Cefotaxime is used for the empiric treatment of meningitis in non-immunocompromised infants and children (in combination with vancomycin and ampicillin pending identification of the causative agent) owing to their excellent activity against Haemophilus influenzae, sensitive Streptococcus pneumoniae, Neisseria meningitides, and gram-negative enteric bacteria. Cefotaxime has excellent activity for the treatment of community-acquired-pneumoniae [1] (Figure 1 and Figure 2).

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "cefotaxime dosing infants, children", cefotaxime efficacy, safety infants, children", "cefotaxime metabolism", "cefotaxime pharmacokinetics infants, children", "cefotaxime

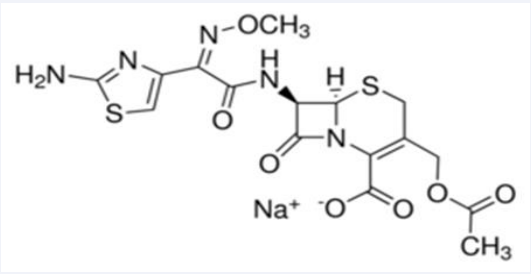

Figure 1 Cefotaxime molecular structure (molecular weight = 455.47 grams/mole).

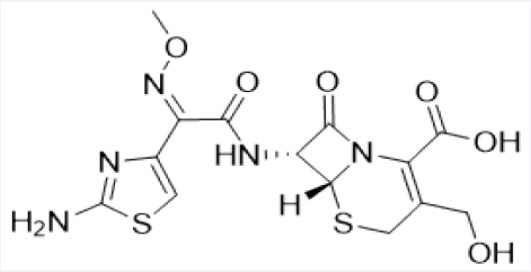

Figure 2 Desacetylcefotaxime molecular structure (molecular weight = 413.4 grams/mole).

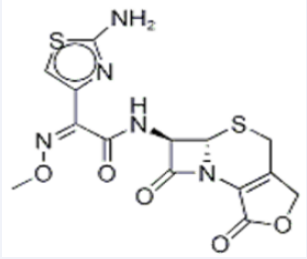

Figure 3 3-Desacetylcefotaxime lactone molecular structure (molecular weight = 395.42).

drug interactions", "cefotaxime treatment infants, children", "cefotaxime penetration into the cerebrospinal fluid infants, children", "cefotaxime treatment of meningitis in infants, children" "cefotaxime placental transfer", and "cefotaxime migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

RESULTS

Administration schedules of cefotaxime to infants and children

Intravenous administration to infants [2]

Infants with a postnatal age of 1 week. Give: 50 mg/kg twice-daily.

Infants with a postnatal age of 2 to 3 weeks. Give: 50 mg/kg thrice-daily.

Infants with a postnatal age longer than 3 weeks. Give: 50 mg/kg 4 times-daily.

The dosage interval should be increased in infants with severe renal failure.

A single intravenous or intramuscular dose of 100 mg/kg can be used to treat neonatal gonococcal eye infection.

The mechanism of action of cefotaxime is the disruption of the bacterial cell wall. The drug distributes widely into the cerebrospinal fluid, bile, bronchial secretions, lung tissue, ascetic fluid, and middle ear. Cefotaxime is metabolized into desacetylcefotaxime which maintains antibacterial activity of the parent compound; it is excreted renally and is incompatible with azithromycin, fluconazole, protamine sulfate, sodium bicarbonate, and vancomycin [3].

Administration schedule to children [4]

Intramuscular treatment of uncomplicated gonorrhoea

Children aged 12 to 17 years. Give: 50 mg/kg thrice-daily (maximum dose = 9 grams daily).

Intravenous treatment of febrile neutropenia

Children. Give: 50 mg/kg thrice-daily (maximum dose = 6 grams daily).

Intravenous treatment of meningitis

Children. Give: 50 mg/kg thrice-daily (maximum dose = 6 grams daily).

Intravenous administration for severe infections due to sensitive gram-positive and gram-negative bacteria

Children. Give: 50 mg/kg thrice-daily (maximum dose = 6 grams daily).

Inhalational treatment of chronic Burkholderia infection in children with cystic fibrosis

Children. Give: 1 gram twice-daily.

Efficacy and safety of cefotaxime in infants and children

The efficacy and safety of cefotaxime were assessed with a dosage of 50 mg/kg 4 times-daily and with 75 mg/kg thrice-daily in infants and children. The dosage of 75 mg/kg thrice-daily is preferable and does not compromise the efficacy and safety of cefotaxime [5]. Cefotaxime has been found efficacy and safe in the treatment of superinfections in children and has the advantage of low rates of complications in hospitalized children [6]. The utilization of cefotaxime in serious bacterial infections in infants and children has become more widely accepted by paediatricians and cefotaxime has been found efficacy and safe in paediatric patients [7]. Cefotaxime and clindamycin was found similarly efficacy than ampicillin, gentamicin, and clindamycin respect to the duration of antibiotic administration, fever, leucocytosis or length of hospitalization in children with ruptured appendicitis [8].

Metabolism of cefotaxime

Following the administration of cefotaxime to humans, cefotaxime was transformed into desacetylcefotaxime and this metabolite was converted into the inactive 3-deseacetylcefotaxime lactone. Other two unidentified metabolites of cefotaxime were detected in human plasma. Desacetylcefotaxime accumulated in plasma when cefotaxime was administered to patients with renal failure [9]. The metabolism of cefotaxime was studied in human haemolysed blood and a the metabolite desacetylcefotaxime was identified [10]. The metabolism of [^{14}C]cefotaxime was studied in-vivo in rats, dogs, and humans. Excretion of radioactivity was similar in all species, and greater than 80% of the dose was recovered in the urine. Approximately one-third of the dose was eliminated unchanged, and the major metabolite was desacetylcefotaxime. Under normal circumstances these two products, both with antibacterial activity, were the only materials detected in the plasma and desacetylcefotaxime was converted into the inactive 3-desacetylcefotaxime lactone. Extensive studies have shown that cefotaxime leads to desacetylcefotaxime and this metabolites leads to the inactive 3-desacetylcefotaxime lactone and the rate-limiting step is the formation of 3-desacetylcefotaxime lactone. Other two unidentified metabolites of cefotaxime were detected in human and animal plasma and urine [11].

Pharmacokinetics of cefotaxime in infants

McCracken et al. [12], studied the pharmacokinetics of cefotaxime in 29 newborn infants, aged 1 to 7 days, who received cefotaxime, ampicillin, and gentamicin. Cefotaxime was intravenously infused at a dose of 50 mg/kg. Infants were divided in two groups, group A consisted in 14 infants aged 4.0 ± 1.6 days and weighing 1,103 ± 216 grams, and infants of group B had a postnatal age of 3.5 ± 1.7 days and weighted 2,561 ± 607 grams. Table 1 shows the serum concentration of cefotaxime in infants of group A and B (Table 1 and Table 2).

Leroux et al. [13], investigated the pharmacokinetics of cefotaxime in 86 newborn infants and older infants with postmenstrual, postnatal age and body-weight of 1,658 ± 905 weeks, 33.3 ± 4.9 days, and 1,815 ± 875 grams, respectively, and cefotaxime was intravenously infused at a dose of 50 mg/kg twice-daily. Table 3 summarizes the pharmacokinetic parameters of cefotaxime which are obtained in these infants.

This table shows that the central distribution volume is similar to the water volume, and the peripheral distribution volume is lower than the central distribution volume suggesting that cefotaxime remains in the blood.

von Hattingberg et al. [14], explored the pharmacokinetics of cefotaxime in 6 infants with a gestational age and body-weight of 34.7 ± 2.1 weeks and 2.047 ± 0.40 grams, respectively, and in two children with a gestational age of 8.0 months and 3.7 years weighing 7.1 and 11.1 kg. Table 4 summarizes the pharmacokinetic parameters of cefotaxime in these infants and children.

Trang et al. [15], studied the pharmacokinetics of cefotaxime and desacetylcefotaxime in 13 infants and children with meningitis and cefotaxime was intravenously infused at a dose of 50 mg/kg 4 times-daily. Cefotaxime and desacetylcefotaxime concentrations were measured in serum and in the cerebrospinal fluid. Table 5 shows the concentrations of cefotaxime and desacetylcefotaxime in serum and in the cerebrospinal fluid (CSF) (Table 5-7).

Interaction of cefotaxime with drugs

Hydrophilic antibiotics such as cefotaxime are potential victims of drug interactions due to transporter inhibition [16]. The co-administration of cefotaxime with sodium-tazobactam induces serious adverse-effects which were rash and prolongation of hospitalization period [17]. Cefotaxime/Streptomycin in 1:10 molar ratio decreases the cefotaxime hydrolysing β-lactamase-15

Table 1: Serum concentration of cefotaxime in infants of groups A and B. Figures are the mean ± SD and (range), by McCracken et al. [12].

	Serum concentration (µg/ml) of cefotaxime		
Time after the end of infusion (hours)	**Infants of group A (N = 14)**	**Infants of group B (N = 15)**	***P-value**
0	116±38.1 (46 – 186)	133±37.5 (76.0 – 208)	0.4159
0.5	95.6±11.2 (72 – 112)	107±38.8 (72.0 – 204)	0.4060
1	83.0±18.6 (48.0 – 122)	85.0±23.7 (77.0 – 128)	0.4159
2	69.8±12.5 (48.0 – 100)	78.9±15.1 (62.0 – 112)	0.4159
4	48.4±13.6 (18.0 – 65.0)	52.2±10.2 (36.0 – 71.0)	0.4159
6	34.4±12.1 (6.0 – 50.0)	38.1±6.9 (30.0 – 49.0)	0.4159

This table shows that cefotaxime decays rapidly after dosing. *Kruskal-Wallis test.

Table 2: Pharmacokinetic parameters of cefotaxime which are obtained in infants of groups A and B. Figures are the mean ± SD, by McCracken et al. [12].

Group of infants	**§Half-life (h)**	**$AUC_{0\text{-}6\ hours}$ (µg*h/ml)**	**DV (ml/g)**	**TBC (ml/min/1.73 m^2)**
Group A	4.63±1.06	400±55.2	510±60	23.0±4.9
Group B	3.37±0.94	392±76.6	440±70	43.9±19.8
*P-value	≤ 0.01	>0.05	≤ 0.01	≤ 0.001

§Elimination half-life. DV = distribution volume. TBC = total body clearance. *Student t test.

Table 3: Final estimates of population pharmacokinetic parameters of cefotaxime and bootstrap analysis results, by Leroux et al. [13].

	Final model		Bootstrap analysis (N = 500)	
Parameter	**Mean estimate**	**%RSE**	**Median**	**95% CI**
TBC	0.21	3.9	0.21	0.20 – 0.23
FGA	2.27	9.4	2.30	1.94 – 2.66
FPNA	0.28	8.2	0.29	0.24 – 0.32
CDV	0.71	12.7	0.70	0.36 – 0.90
PDV	0.35	28.1	0.38	0.19 – 0.89
Q	0.27	38.1	0.26	0.10 – 3.75
%Interindividual variability of total body clearance				
---	21.0	27.7	20.0	14.6 – 25.9
%Residual variability				
---	35.1	13.7	34.3	30.2 – 38.5

TBC = Total body clearance. FGA = gestational age. FPNA = Postnatal age. CVD = central distribution volume. PDV = peripheral distribution volume. Q = intercompartmental clearance. %RSE = %relative standard error. CI = confidence interval. At the time of sampling, the median gestational age, postnatal age, and the body-weight were: 30 weeks, 12 days, and 1,665 grams, respectively.

Table 4: Pharmacokinetic parameters of cefotaxime which are obtained in infants and children. Figures are the mean ± SD in infants and single values in children, by von Hattingberg et al. [14].

	Total body clearance (L/kg/h)	Distribution volume (L/kg)	Elimination half-life (h)
Infants	0.10±0.04	0.42±0.09	3.49±0.70
Child 1	0.47	0.31	0.46
Child 2	0.11	0.16	1.02

Table 5: cefotaxime and desacetylcefotaxime in the serum and CSF. Figures are the mean ± SD and (range), by Trang et al. [15].

Serum concentrations of cefotaxime and desacetylcefotaxime (µg/ml)				
Time after the end of infusion (h)				
0.25	1.0	6.0	CSF concentration of cefotaxime and desacetylcefotaxime (µg/ml)	CSF/Serum ratio (%)
Cefotaxime				
121±23.1 (92.7 – 168)	61.4±26.2 (25.8 – 97.2)	1.6±3.1 (0.0 – 8.2)	6.2±5.0 (0.0 – 18.8)	10.1 (0.0 – 20.0)
Desacetylcefotaxime				
13.3±7.8 (0.0 – 21.5)	19.3±11.2 (8.2 – 28.8)	7.8 ±7.8 (0.0 – 20.5)	5.6±7.3 (0.0 – 23.1)	28.8 (0.0 – 103)

This table shows the serum concentration of cefotaxime is greater than that of desacetylcefotaxime and the concentration of cefotaxime is similar to the concentration of desacetylcefotaxime in the cerebrospinal fluid.

Table 6: Urinary excretion and pharmacokinetic parameters of cefotaxime and desacetylcefotaxime which are obtained in 13 infants and children. Figures are the mean ± SD, by Trang et al. [15].

Urinary excretion (mg)	Urinary excretion/dose (%)	$AUC_{0\text{-}6\ hours}$ (µg/h*kg)	TBC (L/h/kg)
Cefotaxime			
355±223	61.4	213±76.3	0.174±0.09
Desacetylcefotaxime			
205±178	35.5	82.4±49.3	0.363±0.377

TBC = total body clearance. This table shows that both cefotaxime and desacetylcefotaxime are renally excreted, the renal excretion-rate of cefotaxime is greater than that of desacetylcefotaxime, and the total body clearance of cefotaxime is lower than that of desacetylcefotaxime.
This table shows that cefotaxime distribution volume is greater in infants than in the two children and the elimination half-life is longer in infants than in children. Cefotaxime is cleared by metabolism and by renal route and both elimination pathways are better expressed in children than in infants.

gene efficiency significantly because of the fact that streptomycin induced structural changes in the cefotaxime hydrolysing β-lactamase-15 gene hence cefotaxime was not properly bound on its active site for hydrolysis rather available for the target to inhibit Enterobacteriaceae [18]. The checkerboard method was used to determine the antimicrobial activity of cefotaxime combined with ofloxacin against 217 bacterial isolates causing serious infections. Synergy or partial synergy was observed against 19 of 34 (55.8%), Staphylococcus aureus methicillin-susceptible isolates, 4 of 47 (8.4%) Streptococcus pneumoniae isolates, 28 of 34 (82.2%), Escherichia coli isolates and 70 of 102 (68.5%) Pseudomonas aeruginosa isolates. Antagonism was not observed with any of the isolates examined [19].

Treatment with cefotaxime in infants and children

Cefotaxime is a suitable alternative to the aminoglycosides for the management of suspected sepsis in the newborn infants

Table 7: Comparison of cefotaxime pharmacokinetic parameters calculated by using model-dependent and non-compartmental methods for 13 infants and children with meningitis. Figures are the mean ± SD, by Trang et al. [15].

Elimination rate constant (h^{-1})	Elimination half-life (h)	Distribution volume at steady-state (L/kg)	Total body clearance (L/h/kg)	Renal clearance (L/h/kg)
Model dependent method				
0.987±0.338	0.79	0.316±0.109	0.268±0.109	---
Non-compartmental method				
0.954±0.381	0.81	0.361±0.197	0.289±0.115	0.174±0.094

This table shows that the model-dependent and the non-compartmental methods generate similar pharmacokinetic parameters of cefotaxime and that the renal clearance is smaller than the total body clearance. Cefotaxime is cleared from the body by both metabolism and renal route, thus the total body clearance accounts for the cefotaxime elimination by metabolism and renal route. Since cefotaxime is mainly eliminated by kidney (70%) and to a lesser extent is converted to desacetylcefotaxime, renal maturation is expected to have a major impact on cefotaxime clearance. Moreover, while renal maturation is completed by about one year of age, the metabolic pathway responsible for the biotransformation of cefotaxime is already active at 27 to 28 weeks of gestational age. The interindividual variability of cefotaxime total body clearance is explained by the wide range of the gestational and postnatal ages, reflecting the influence of both antenatal and postnatal maturation.

[20]. The recommend dosing of cefotaxime is as follows: 25 mg/kg twice-daily for preterm infants aged < one week of age, thrice-daily for preterm infants aged one to 4 weeks, and term infants aged < one week of age, and every 4 times-daily for term infants aged > one week [21]. Treatment with cefotaxime was effective against multidrug resistant Haemophilus influenzae [22]. Standard intermittent cefotaxime dosing-regimens in critically ill children are not adequate to reach the target. Continuous infusion was the only administration that enabled the target to be attained for children aged > 1 month. As the continuous administration is achievable in the paediatric intensive care unit it should be considered for clinical practice [23]. Cefotaxime is efficacy in the treatment of children with complicated urinary-tract, lower respiratory-tract infections, bacteraemia, meningitis, uncomplicated gonorrhoea, and skin, soft-tissue, bone, joints, obstetric and gynaecologic infections [24]. Treatment with cefotaxime is appropriate in children with urinary-tract infections [25]. Cefotaxime alone is the appropriate therapy for conditions previously treated with aminoglycosides (other than Pseudomonal infections). Cefotaxime offers potentially important clinical and practical advantages, is free of serious adverse-effects, and freedom from the need to undertake drug plasma concentration monitoring [26]. Cefotaxime is effective in the treatment of children with serious infections caused by gram-positive and gram-negative organisms [27]. Optimal cefotaxime dosing-regimen are: 25 mg/kg twice-daily in the first 7 days of life, thrice-daily in the first 3 weeks of life, and 4 times-daily in older infants and children [28].

Penetration of cefotaxime into the cerebrospinal fluid of infants and children (CSF)

Cefotaxime plasma and CSF concentrations were measured in 30 infants and ranged from 2.30 to 175.42 μg/ml in plasma and from 0.39 to 25.38 μg/ml in the cerebrospinal fluid, and the median ratio of the CSF to the plasma concentration was 0.28 (range, 0.06 to 0.76) [29]. Two grams of cefotaxime were intravenously infused to 6 children with inflamed meninges and the concentration of cefotaxime in the CSF ranged from 0.14 to 1.81 μg/ml at a median time of 3 hours following the end of infusion. The elimination half-life of cefotaxime in the CSF ranged between 5.0 to 26.9 hours (median, 9.3). The concentration of cefotaxime in the CSF reliably inhibits the growth of staphylococci and penicillin G-resistant Streptococcus pneumoniae [30]. Ninety Children with bacterial meningitis were treated with cefotaxime at a dose of 300 mg/kg daily and with vancomycin at a dose of 60 mg/kg daily. The median concentrations of cefotaxime and desacetylcefotaxime in the CSF were 4.4 and 3.2 μg/ml, respectively [31]. Fourteen children, aged 9 days to 5 years, with bacterial meningitis received cefotaxime at a dose of 40 mg/kg daily and cefotaxime and desacetylcefotaxime were measured in the plasma and in the CSF (Table 8).

Thirty-three children with bacterial meningitis were treated with cefotaxime at a dose of 50 mg 4 times-daily and the mean concentration of ceftizoxime in the CSF was 0.45μg/ml and it ranged within a wide interval according to the post-dose interval and the duration of illness [32].

Treatment of meningitis with cefotaxime in infants and children

Le Saux [33], reported the guidelines for treatment of bacterial meningitis in infants aged > 1 month. Cefotaxime dosage is 75 mg/kg 4 times-daily and the maximal dose is 4 grams twice-daily [34]. Feldstein et al. [34], reviewed the efficacy of cefotaxime in treating the meningitis caused by gram-negative bacteria. Cefotaxime displayed excellent activity against ampicillin-resistant β-lactamase producing Haemophilus influenzae. Cefotaxime was 98.6% effective for the three most commonly encountered gram-negative meningeal pathogens. Cefotaxime was used as a single agent in 75.0% of the reported cases and the overall cure-rate against all gram-negative isolates was 96.3% [35]. Salmonella typhimurium is the commonest organism causing meningitis and 89.7% of the infections occur in children aged < 1 year and cefotaxime has a cure-rate of 84.6% [36]. Cefotaxime was administered to 47 children, aged 22.8 ± 25.3 months with bacterial meningitis caused by Haemophilus influenzae type b, Neisseria meningitides, Streptococcus pneumoniae, Escherichia coli, Streptococcus agalactiae, and Salmonella species and cefotaxime is safe and efficacy in the treatment of bacterial meningitis [37]. Cefotaxime was administered at a dose of 200 mg/kg daily for 7 days to 38 infants and children, aged 6 weeks to 16 years, with bacterial meningitis and full recovery was observed in 71.1% of children [38]. Eighty-five infants and children with bacterial meningitis were treated with cefotaxime and the meningitis was cured in all children [39].

Table 8: This table shows the concentrations of cefotaxime and desacetylcefotaxime in the plasma and in the CSF. Figures are the mean ± SD and (range), by Asmar et al. [32].

Cefotaxime and desacetylcefotaxime concentrations (µg/ml)					
Early sampling (36 to 48 hours)			**Late sampling (14 days)**		
Plasma	**CSF**	**Penetration ratio (%)**	**Plasma**	**CSF**	**Penetration ratio (%)**
Cefotaxime					
16.7±14.7 (5.1 – 55.7)	6.0±10.2 (0.74 – 38.8)	27.7±16.2 (7.0 – 39.7)	6.6±4.3 (1.7 – 13.6)	1.2±0.9 (0.6 – 3.1)	25.7±21.0 (4.5 – 64.7)
Desacetylcefotaxime					
8.1±4.2 (2.5 – 20.1)	4.6±7.0 (0.89 – 27.4)	51.9±54.5 (12.2 – 219)	5.4±1.9 (1.5 – 9.5)	1.1±0.8 (0.5 – 2.1)	20.8±9.3 (8.9 – 40.0)
This table shows that the penetration ratio of desacetylcefotaxime into the cerebrospinal fluid is higher than that of cefotaxime. The penetration ratio of cefotaxime is similar at the early and late sampling times whereas that of desacetylcefotaxime is higher at early than late sampling times.					

Placental transfer of cefotaxime in women

In literature there is only a study on the placental transfer of cefotaxime and it has been reported by Lepercq et al. [39]. Eight pregnant women were treated with cefotaxime at a dose of 2 grams at the onset of labour, then 1 gram 6 times-daily until delivery and cefotaxime concentration was measured in maternal and umbilical cord blood. The maternal infective agents were Streptococcus marcescens, Escherichia coly and Klebsiella pneumonia (Table 9 and Table 10).

Migration of cefotaxime into the breast-milk

Cefotaxime was given as an intravenous bolus injection at a dose of 1 gram to 42 breastfeeding women and the concentration of cefotaxime in the beast-milk averaged to 0.32 ± 0.09 µg/ml 2 hours after dosing. The milk to serum ratio of cefotaxime concentration increases as the serum concentrations diminishes [40]. The migration of cefotaxime into the breast-milk was studied in 12 breastfeeding women who received 1 gram of cefotaxime. This drug peaked in the breast-milk 2 to 3 hours after dosing and the peak concentration ranged from 0.25 to 0.52 µg/ml. Cefotaxime concentration in the breast-milk could affect the oropharyngeal flora of the suckling infant [41].

DISCUSSION

Cefotaxime is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative bacteria. Cefotaxime is active against Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus, and Streptococcus pyogenes. Cefotaxime is used for the empiric treatment of meningitis in non-immunocompromised infants and children owing to the excellent activity against Haemophilus influenzae, sensitive Streptococcus pneumoniae, Neisseria meningitides, gram-negative enteric bacteria, and community-acquired-pneumoniae. For the treatment of meningitis caused by these organisms, cefotaxime is associated with vancomycin and ampicillin [1]. Cefotaxime is administered intravenously or intramuscularly and the dose is 50 mg/kg twice-daily, thrice-daily or 4 time-daily in infants with the postnatal age of 1 week, 2 to 3 weeks, and > 3 weeks, respectively [2]. In children the dose is 50 mg/kg thrice-daily [4]. Cefotaxime has been found efficacy and safe in infants and in children [5-8]. In infants, cefotaxime dosage of 75 mg/kg thrice-daily is more efficacy and safe than

Table 9: Cefotaxime doses and cefotaxime concentrations in the maternal and umbilical cord blood. Figures are the mean ± SD and (range), by Lepercq et al. [39].

Intrapartum				
Cefotaxime concentration (µg/ml)			**Delivery**	
30 min	Mother	Umbilical cord	Time (min) from last administration to delivery	Cord to mother concentration ratio of cefotaxime (%)
44.1±8.6 (15.3 – 63.6)	9.7±4.6 (1.95 – 35.3)	4.1±1.3 (0.72 – 8.49)	111±28.2 (15 – 225)	77.0±23.7 (5 – 172)
30 min = blood specimens were collected 30 min after the first administration. This table shows that cefotaxime crosses the human placenta and achieves significant concentrations in the umbilical cord blood.				

Table 10: Desacetylcefotaxime concentrations measured in the mother and umbilical cord blood. Figures are the mean ± SD and (range), by Lepercq et al. [39].

Desacetylcefotaxime concentrations in the maternal and umbilical cord blood (µg/ml)			
Intrapartum		**Delivery**	
30 min	Mother	Umbilical cord	Cord to mother concentration ratio of desacetylcefotaxime (%)
10.9±1.3 (4.77 – 14.1)	62±0.9 (3.17 – 10.2)	5.5±1.1 (3.15 – 12.2)	99.4±20.1 (31 – 187)
30 min = blood specimens were collected 30 min after the first administration. This table shows that desacetylcefotaxime freely crosses the placenta and reaches similar concentrations in the maternal and umbilical cord blood.			

50 mg/kg 4 times-daily [5]. This antibiotic is efficacy and safe in the treatment of superinfections in children [6], in the treatment of infections in paediatric patients [7], and the combination of cefotaxime with clindamycin is effective for the treatment of fever, leucocytosis and reduces the hospitalization length in children with ruptured appendicitis and it is similarly efficacy than ampicillin, gentamicin, and clindamycin [8]. Cefotaxime is metabolized into desacetylcefotaxime in-vivo and this metabolite maintains the antibacterial activity of the parent compound [9-11], desacetylcefotaxime is converted into the inactive 3-desacetylcefotaxime lactone, two unidentified metabolites were isolated from the human plasma [9,11], and about one-third of cefotaxime dose is excreted unchanged in the urine [11]. The pharmacokinetics of cefotaxime were studied in infants and McCracken et al. [12], observed that cefotaxime serum concentration rapidly decreases in infant serum. These authors clustered the infants into two groups, based on the body-weight, and the mean half-life is 4.63 and 3.37 hours and the total body clearance is 23.0 and 43.9 ml/min/1.73 m^2 in these two groups of infants. The cefotaxime half-life decreases and the total body clearance increases in infants with higher body-weight. The pharmacokinetics of cefotaxime were studied in 13 infants and children, the half-life and the total body clearance of cefotaxime are about 0.8 hours and about 0.3 L/h/kg, respectively, the renal clearance of cefotaxime is about one half of the total body clearance, and the distribution volume is about 0.3 L/kg [15]. Cefotaxime is cleared from the body by renal route and by metabolism and these elimination pathways are greater in children than in infants because they increase with the infant maturation and child development. The urinary excretion-rate to dose ratio is 61.4% for cefotaxime and 35.3% for desacetylcefotaxime and the total body clearance of desacetylcefotaxime is greater than that of cefotaxime [15]. Cefotaxime interacts with drugs [16-19]. Cefotaxime inhibits the transport of drugs [16], cefotaxime co-administered with sodium-tazobactam induces rash and prolongs the hospitalization period [17], streptomycin decreases the cefotaxime hydrolysing β-lactamase-15 gene [18], and cefotaxime combined with ofloxacin produces a synergistic activity in isolates of Staphylococcus aureus methicillin-susceptible, Streptococcus pneumoniae, Escherichia coli, and Pseudomonas aeruginosa [19]. The treatment with cefotaxime was studied in infants and children [20-28]. Cefotaxime is an alternative to the aminoglycosides for the management of sepsis in infants [20], Kafetzis et al. [21], provided the dosing-regimens for infants with different postnatal ages. Cefotaxime is effective in the treatment of multidrug resistant Haemophilus influenzae [22]. Continuous infusion of cefotaxime is more adequate than intermittent administration for the treatment of bacterial infections in infants and children [23]. Cefotaxime is efficacy in the treatment of children with complicated urinary-tract, lower respiratory-tract infections, bacteraemia, meningitis gonorrhoea, and skin, soft-tissue, bone, joints, obstetric and gynaecologic infections [24]. Cefotaxime is the appropriate treatment of children with urinary-tract infections [25]. Cefotaxime alone is the appropriate therapy for conditions previously treated with aminoglycosides, offers clinical and practical advantages and is free from serious adverse-effects [26]. Cefotaxime is effective in the treatment of children with serious infections caused by gram-positive and gram-negative organisms [27]. Papadatos et al. [28], provided the cefotaxime dosing-regimens for the treatment of serious infections in infants and children. The penetration of cefotaxime into the cerebrospinal fluid has been extensively studied in infants and children [29-33]. The concentrations of cefotaxime range from 2.30 to 175.4 in the plasma and from 0.39 to 25.30 μg/ml in the cerebrospinal fluid, the median cerebrospinal fluid to plasma ratio for cefotaxime is 0.28 (range, 0.06 to 0.73), and the cefotaxime elimination half-life in the cerebrospinal fluid ranges from 5.0 to 26.9 hours (median, 9.3) [29]. Cefotaxime inhibits the growth of staphylococci and penicillin G-resistant Streptococcus pneumoniae In the cerebrospinal fluid [30]. The penetration of cefotaxime into the cerebrospinal fluid was studied by Asmar et al. [32], and following prolonged treatment with cefotaxime, the cerebrospinal fluid to plasma ratio is 25.7% for cefotaxime and 20.8% for desacetylcefotaxime [32]. Children treated with cefotaxime at a dose of 50 mg/kg 4 times-daily have a mean cefotaxime concentration fluid of 0.45 μg/ml in the cerebrospinal [33]. The treatment of meningitis with cefotaxime has been studied in infants and children [33-39]. Le Saux [33], reported the guidelines for the treatment of bacterial meningitis in infants, and Feldstein et al. [34] observed that cefotaxime is efficacy in the treatment of meningitis due to ampicillin-resistant β-lactamase producing Haemophilus influenzae and it is effective for more than 90% cases of meningitis caused by gram-negative organisms. Cefotaxime cures the meningitis caused by gram-negative bacteria in more than 90% children [35], cures the meningitis due to Salmonella typhimurium [36], and the meningitis caused by Haemophilus influenzae type b, Neisseria meningitides, Streptococcus pneumoniae, Escherichia coli, Streptococcus agalactiae, and Salmonella species in children [37]. Cefotaxime administered to a dose if 200 mg daily for 7 days cures the bacterial meningitis in children [38], and infants and children with bacterial meningitis were cured with cefotaxime [39]. Cefotaxime crosses the human placenta and the umbilical cord to mother blood ratio is 77.0% for cefotaxime and 99.4% for desacetylcefotaxime [39], and cefotaxime migrates into the breast-milk in significant amounts [40,41].

In conclusion, cefotaxime is resistant to many narrow-spectrum β-lactamases and is active against most gram-positive and gram-negative bacteria. In particular, cefotaxime is active against Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, and Streptococcus pyogenes. Cefotaxime is administered intravenously or intramuscularly and the dose of cefotaxime is 50 mg/kg twice-daily, thrice-daily or 4 times-daily to infants with a postnatal age of 1 week, 2 to 3 weeks and > 3 weeks, respectively, and in children the dose is 50 mg/kg thrice-daily. Cefotaxime is metabolized into desacetylcefotaxime, which maintains the antibacterial activity of the parent compound, and desacetylcefotaxime is converted into the inactive 3-desacetylcefotaxime lactone. The elimination half-life of cefotaxime is about 4 hours in infants and about 0.8 hours in children. In infants, the total body clearance and the renal clearance of cefotaxime are 0.289 and 0.174 L/h/kg, respectively. The treatment with cefotaxime has been extensively studied in infants and children; this antibiotic penetrates into the cerebrospinal fluid in significant amounts and cures the meningitis caused by different organisms in infants and children. Cefotaxime and

desacetylcefotaxime crosses the human placenta and the umbilical cord to maternal blood ratio is 70.0 and 99.4% for cefotaxime and desacetylcefotaxime, respectively, and cefotaxime migrates into the breast-milk in significant amounts. The aim of this study is the review of the clinical pharmacology of cefotaxime 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.

ACKNOWLEDGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

REFERENCES

1. MacDougal C. Penicillins, Cephalosporins, and other β-Lactam Antibiotics. In The Goodman & Gilman's. The Pharmacological Basis of the Therapeutics, Brunton Hilal-dandan LL, Knollmann BC, Eds. Mc Graw Hill, 13th Edition, USA, New York. 2018; 1023-1038.
2. Neonatal Formulary. Cefotaxime. Oxford University Press. 8th Edition, Great Clarendon Street, Oxford, OX2, 6DP, UK. 2020; 180-182.
3. Young TE, Mangum B. NEOFAX®. Cefotaxime. Thomas Reuters Clinical Editorial Staff, 23rd Edition, Montvale, USA. 2010; 26-27.
4. The British national formulary for children. Cefotaxime. Macmillan, 78th Edition, Hampshire International Business Park, Hampshire, Lime Three Way, Basingstoke, Hampshire, UK. 2020; 330-331.
5. Kearns GL, Young RA, Jacobs RF. Cefotaxime dosage in infants and children. Pharmacokinetic and clinical rationale for an extended dosage interval. Clin Pharmacokinet. 1992; 22: 284-297.
6. Jacobs RF, Darville T, Parks JA, Enderlin G. Safety profile and efficacy of cefotaxime for the treatment of hospitalized children. Clin Infect Dis. 1992; 14: 56-65.
7. Jacobs RF. Efficacy and safety of cefotaxime in the management of pediatric infections. Infection. 1991; 19: S330-336.
8. Schropp KP, Kaplan S, Golladay ES, King DR, Pokorny W, Mollitt DL, et al. A randomized clinical trial of ampicillin, gentamicin and clindamycin versus cefotaxime and clindamycin in children with ruptured appendicitis. Surg Gynecol Obstet. 1991; 172: 351-356.
9. Reeves DS, White LO, Holt HA, Bahari D, M. Bywater MJ, Bax RP. Human metabolism of cefotaxime. J Antimicrb Chemother. 1980; 6: 93-101.
10. Welch WD, Bawdon RE. Cefotaxime metabolism by hemolyzed blood: Quantitation and inhibition of the deacetylation reaction. Diagn Microbiol Infect Dis. 1986; 4: 119-124.
11. Coombes JD. Metabolism of cefotaxime in animals and humans. Rev Infect Dis. 1982; 4: S325-332.
12. McCracken GH Jr, Threlkeld NE, Thomas ML. Pharmacokinetics of cefotaxime in newborn infants. Antimicrob Agents Chemother. 1982; 21: 683-684.
13. Leroux S, Roué JM, Gouyon JB, Biran V, Zheng H, Zhao W, et al. A Population and Developmental Pharmacokinetic Analysis to Evaluate and Optimize Cefotaxime Dosing-regimen in Neonates and Young Infants. Antimicrob Agents Chemother. 2016; 60: 6626-6634.
14. von Hattingberg HM, Marget W, Belohradsky BH, Roos R. Pharmacokinetics of cefotaxime in neonates and children: clinical aspects. J Antimicrob Chemother. 1980; 6: 113-118.
15. Trang JM, Jacobs RF, Kearns GL, Brown AL, Wells TG, Underwood FL, et al. Cefotaxime and desacetylcefotaxime pharmacokinetics in infants and children with meningitis. Antimicrob Agents Chemother. 1985; 28: 791-795.
16. Yu X, Chu Z, Li J, He R, Wang Y, Cheng C. Pharmacokinetic Drug-drug Interaction of Antibiotics Used in Sepsis Care in China. Curr Drug Metab. 2021; 22: 5-23.
17. Chen N, Sun LN, Hu WH, Wang YY, Xie LJ, Cheng J, et al. Tolerability, Safety, Pharmacokinetics and Drug Interaction of Cefotaxime Sodium-Tazobactam Sodium Injection (6:1) Following Single and Multiple Intravenous Doses in Chinese Healthy Subjects. Front Pharmacol. 2020; 11: 1033.
18. Maryam L, Khan U. A Mechanism of Synergistic Effect of Streptomycin and Cefotaxime on CTX-M-15 Type β-lactamase Producing Strain of E. cloacae: A First Report. Front Pharmacol. 2016; 7: 2007.
19. Gimeno C, Borja J, Navarro D, Valdés L, García-Barbal J, García-de-Lomas J. In vitro interaction between ofloxacin and cefotaxime against gram-positive and gram-negative bacteria involved in serious infections. Chemotherapy. 1998; 44: 94-98.
20. Hall MA, Beech RC, Seal DV. The use of cefotaxime for treating suspected neonatal sepsis: 2 years' experience. J Hosp Infect. 1986; 8: 57-63.
21. Kafetzis DA, Brater DC, Kapiki AN, Papas CV, Dellagrammaticas H, Papadatos CJ. Treatment of severe neonatal infections with cefotaxime. Efficacy and pharmacokinetics. J Pediatr. 1982; 100: 483-489.
22. Su PY, Huang AH, Lai CH, Lin HF, Lin TM, Ho CH. Extensively drug-resistant Haemophilus influenzae - emergence, epidemiology, risk factors, and regimen. BMC Microbiol. 2020; 20: 102.
23. Béranger A, Oualha M, Urien S, Genuini M, Renolleau S, Aboura R, et al. Population Pharmacokinetic Model to Optimize Cefotaxime Dosing-regimen in Critically Ill Children. Clin Pharmacokinet. 2018; 57: 867-875.
24. Todd PA, Brogden RN. Cefotaxime. An update of its pharmacology and therapeutic use. Drugs. 1990; 40: 608-651.
25. Nickavar A, Sotoudeh K. Treatment and prophylaxis in pediatric urinary tract infection. Int J Prev Med. 2011; 2: 4-9.
26. Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Cefotaxime. A review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs. 1983; 25: 223-289.
27. Kaplan SL. Serious pediatric infections. Am J Med. 1990; 88: 18S-24S.
28. Papadatos CJ, Kafetzis DA, Kanarios J. Cefotaxime in the treatment of severe paediatric infections. J Antimicrob Chemother. 1980; 6: 243-248.
29. Chen XK, Shi HY, Leroux S, Xu HY, Zhou Y, Zheng Y, et al. Penetration of Cefotaxime into Cerebrospinal Fluid in Neonates and Young Infants. Antimicrob Agents Chemother. 2018; 62: e02448-02457.
30. Doit C, Barre J, Cohen R, Bonacorsi S, Bourrillon A, Bingen EH. Bactericidal activity against intermediately cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with bacterial meningitis treated with high doses of cefotaxime and vancomycin. Antimicrob Agents Chemother. 1997; 41: 2050-2052.
31. Asmar BI, Thirumoorthi MC, Buckley JA, Kobos DM, Dajani AS. Cefotaxime diffusion into cerebrospinal fluid of children with meningitis. Antimicrob Agents Chemother. 1985; 28: 138-140.

32. Goldwater PN. Cefotaxime and ceftriaxone cerebrospinal fluid levels during treatment of bacterial meningitis in children. Int J Antimicrob Agents. 2005; 26: 408-411.

33. Le Saux N. Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age. Paediatr Child Health. 2014; 19: 141-146.

34. Feldstein TJ, Uden DL, Larson TA. Cefotaxime for treatment of gram-negative bacterial meningitis in infants and children. Pediatr Infect Dis J. 1987; 6: 471-475.

35. 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.

36. Sáez-Llorens X, Castaño E, García R, Báez C, Pérez M, Tejeira F, et al. Prospective randomized comparison of cefepime and cefotaxime for treatment of bacterial meningitis in infants and children. Antimicrob Agents Chemother. 1995; 39: 937-940.

37. Scholz H, Hofmann T, Noack R, Edwards DJ, Stoeckel K. Prospective comparison of ceftriaxone and cefotaxime for the short-term treatment of bacterial meningitis in children. Chemotherapy. 1998; 44: 142-147.

38. Odio CM, Faingezicht I, Salas JL, Guevara J, Mohs E, McCracken GH Jr. Cefotaxime vs. conventional therapy for the treatment of bacterial meningitis of infants and children. Pediatr Infect Dis. 1986; 5: 402-407.

39. Lepercq J, Treluyer JM, Auger C, Raymond J, Rey E, Schmitz T, et al. Evaluation of cefotaxime and desacetylcefotaxime concentrations in cord blood after intrapartum prophylaxis with cefotaxime. Antimicrob Agents Chemother. 2009; 53: 2342-2345.

40. Kafetzis DA, Siafas CA, Georgakopoulos PA, Papadatos CJ. Passage of cephalosporins and amoxicillin into the breast milk. Acta Paediatr Scand. 1981; 70: 285-288.

41. Kafetzis DA, Lazarides CV, Siafas CA, Georgakopoulos PA, Papadatos CJ. Transfer of cefotaxime in human milk and from mother to foetus. J Antimicrob Chemother. 1980; 6: 135-141.

Cite this article

Pacifici GM (2021) Clinical Pharmacology of Cefotaxime in Infants and Children. J Pharmacol Clin Toxicol 9(1):1153.