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Clinical pharmacology of cefuroxime

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RESEARCH ARTICLE

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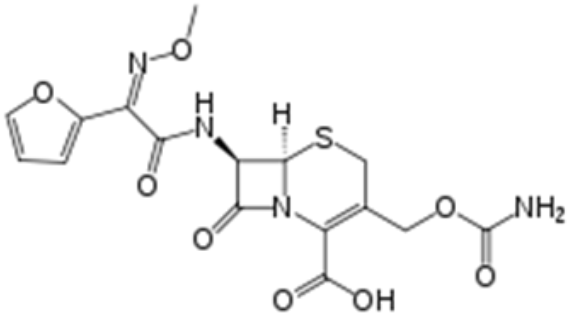
Abstract: Cefuroxime is a second-generation cephalosporin and is active against Haemophilus influenzae (including strains resistant to ampicillin), Neisseria meningitidis, and Streptococcus pneumoniae and the activity against Escherichia coli and Klebsiella is modest. Cefuroxime axetil is 1-acetyloxyethyl ester of cefuroxime and between 30% and 50% of cefuroxime axetil is absorbed following oral administration. The efficacy and safety of cefuroxime axetil have been extensively reported. The diffusion of cefuroxime into human body-tissues has been studied and cefuroxime peak concentration in muscle and in subcutaneous tissue is about one-third of that in plasma and cefuroxime peak concentration in brain is about 10% of that in plasma. The pharmacokinetics of cefuroxime axetil have been studied, the elimination half-life of cefuroxime axetil is about 1 hour, and cefuroxime axetil is eliminated in the urine. The prophylaxis, treatment, and trials with cefuroxime axetil have been extensively studied. Cefuroxime penetrates into the cerebrospinal fluid is significant amounts, the concentration of cefuroxime in cerebrospinal fluid is about 10% of that in serum, cefuroxime sterilizes the cerebrospinal fluid, and cefuroxime treats bacterial meningitis. Some bacteria may become resistant to cefuroxime. Cefuroxime freely crosses the human placenta and poorly migrates into the breast-milk. The aim of this study is to review cefuroxime axetil efficacy and safety, diffusion of cefuroxime into body-tissues, cefuroxime axetil pharmacokinetics, prophylaxis, treatment, trials, cefuroxime penetration into the cerebrospinal fluid, treatment of bacterial meningitis, transfer across the human placenta,and migration into the breast-milk, and resistance of bacteria to cefuroxime.

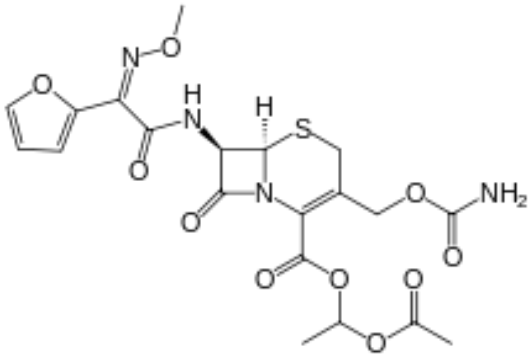
Keywords: *breast-milk, cefuroxime, cerebrospinal-fluid, efficacy-safety, meningitis, pharmacokinetics, placenta, prophylaxis, resistance, tissue-concentration, treatment, trials.*

1. INTRODUCTION

Cefuroxime is a second-generation cephalosporin and has good activity against Haemophilus influenzae (including strains resistant to ampicillin), Neisseria meningitidis, and Streptococcus pneumoniae. Activity against Escherichia coli and Klebsiella is modest. Antistaphylococcal activity is inferior to first-generation cephalosporins. Unlike cefoxitin, cefotetan, and cefmetazole, cefuroxime lacks activity against Bacillus fragilis. Cefuroxime can be given orally, intravenously, or intramuscularly every 8 to 12 hours. Cefuroxime concentrations in cerebrospinal fluid are about 10% of those in plasma, and cefuroxime is effective but inferior to ceftriazone for the treatment of bacterial meningitis due to susceptible organisms. Cefuroxime axetil is 1-acetyloxyethyl ester of cefuroxime. Between 30% and 50% of an oral dose is absorbed, and the drug then is hydrolysed to cefuroxime; resulting concentrations in plasma are variable [1].



Cefuroxime molecular structure (molecular weight = 424.38 grams/mole)



Cefuroxime axetil molecular structure (molecular weight = 510.47 grams/mole)

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Literature search

The literature search was performed electronically using PubMed database as search engine and the following keywords were used: “cefuroxime efficacy safety”, “cefuroxime tissue concentration”, “cefuroxime pharmacokinetics”, “cefuroxime prophylaxis” “cefuroxime treatment”, “cefuroxime trials”, cefuroxime CSF”, “cefuroxime meningitis”, “cefuroxime resistance”, “cefuroxime placental transfer”, and “cefuroxime breast-milk”. In addition, the book “The pharmacological basis of therapeutics” [1] has been consulted.

Results

Efficacy and safety of cefuroxime axetil or cefuroxime

Extended-release cefuroxime axetil tablets administered once-daily were comparable in efficacy, safety and tolerability to cefixime tablets administered twice-daily in patients with acute tonsillopharyngitis [2]. A 4-day treatment with cefuroxime axetil was effective and well-tolerated as the conventional 10-day treatment with penicillin in children with acute group A β-haemolytic Streptococcus pharyngitis [3]. Cefuroxime axetil is efficacy, safety, and well tolerable in children with respiratory-tract or soft-tissue infections [4]. Cefuroxime with axetil administered at a dose of 250 mg twice-daily, is safe and effective as augmentin administered at a dose of 375 mg thrice-daily in the treatment of upper respiratory-tract infections [5]. Cefuroxime axetil administered at a dose of 250 mg twice-daily is effective as amoxicillin/clavulanate administered at a dose of 500 mg thrice-daily in treatment of acute sinusitis [6]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, is as efficacy and safe as amoxicillin/clavulanate administered at a dose of 500 mg thrice-daily in the treatment of acute bacterial maxillary sinusitis [7]. Treatment was clinically successful in 90.4% of patients in the levofloxacin group and in 90.6% of patients in the cefuroxime group thus levofloxacin is similarly efficacy as cefuroxime in treating exacerbation of chronic obstructive pulmonary disease [8]. Cefuroxime is efficacy and safe in the treatment of acute pyelonephritis during pregnancy [9]. Cefuroxime monotherapy is efficacy and safe as cefuroxime plus gentamicin in treating faecal flora infection [10].

The concentration of cefuroxime in body-tissues

Skhirtladze-Dworschak et al. [11] measured the cefuroxime concentration in different body-tissues in 12 patients undergoing cardiac surgery. Six patients, aged 63±15 years and with a body-mass-index of 23±2 kg/m^2, received 1.5 grams of cefuroxime as bolus infusion before surgery and 12 and 24 hours thereafter (group A), and 6 patients, aged 69±15 years and with a body-mass-index of 26±3 kg/m^2, received cefuroxime as a continuous infusion of 1.5 grams of cefuroxime (group B).

Table 1. Pharmacokinetic parameters of cefuroxime which have been obtained in plasma and in the interstitial space fluid of muscle and subcutaneous tissue. Values are the median and (interquartile range) by Skhirtladze-Dworschak et al. [11].

Variable	Patients of group A	Patients of group B	*P-value
Area under the concentration-time curve (µg*h/ml)			
Plasma $_{0\text{-}32\ h}$	338 (233 – 391)	542 (438 – 682)	0.026
Free plasma $_{0\text{-}32h}$	257 (177 – 297)	399 (333 – 518)	0.026
Muscle tissue $_{0\text{-}12h}$	49 (45 – 67)	81 (48 – 113)	0.240
Subcutaneous tissue $_{0\text{-}12h}$	42 (39 – 47)	78 (61 – 113)	0.041
Muscle/plasma ratio $_{0\text{-}12h}$	0.46 (0.44 – 0.73)	0.29 (0.22 – 0.46)	0.065
Peak concentration (µg/ml)			
Plasma	77 (70 – 85)	90 (83 – 97)	0.180
Free plasma	58 (53 – 79)	68 (63 – 73)	0.394
Muscle tissue	26 (23 – 28)	32 (22 – 43)	0.394
Subcutaneous tissue	21 (19 – 29)	33 (26 – 38)	0.580
Time to reach the peak concentration (h)			
Plasma	0.17 (0.17 – 0.17)	0.17 (0.08 – 0.17)	0.065

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Free plasma	0.17 (0.17 – 0.17)	0.17 (0.08 – 0.17)	0.065
Muscle tissue	1.1 (0.2 – 1.4)	0.7 (0.2 – 1.0)	0.699
Subcutaneous tissue	1.1 (0.4 – 1.2)	1.1 (1.0 – 1.2)	0.818

*Wilcoxon signed rank test.

This table shows that cefuroxime AUC value and peak concentration are lower in muscle and subcutaneous tissue than in plasma and cefuroxime rapidly diffuses in muscle and in subcutaneous tissue as Tmax is 1.1 hour. Cefuroxime AUC value in plasma is greater in patients of group B, and cefuroxime AUC value and the peak concentration are similar in patients of groups A and B.

Hosmann et al. [12] measured cefuroxime concentration in the brain. Free interstitial concentrations of cefuroxime after intravenous application of 1.5 grams were measured by microanalysis in brain tissue, as well as in plasma at steady-state (N = 6) or after single-dose administration (N = 1). Patients were aged 52.7±14.3 years, weighed 75.3±10.2 kg, and had a body-mass-index of 26.2±4.5 kg/m^2.

Table 2. Pharmacokinetic parameters of cefuroxime which have been obtained at steady-state in 7 patients. Values are the mean±SD, by Hosmann et al. [12].

	AUC (µg*h/ml)		AUC brain/ AUC free plasma ratio	Peak conc. (µg/ml)	Tmax (h)	*Half-life (h)	TBC (L/h)	DV (L)
Compartment	AUC_{0-8h}	AUC_{0-24h}						
Plasma total	189±102	568±307	---	87.7±51.6	1.0	3.3±1.0	9.0±4.8	35.3±1.9
Plasma fee	130±70.1	389±210	---	60.1±35.4	1.0	3.1±1.0	---	---
Brain	43.8±24.3	131±72.8	0.3±0.1	6.3±3.3	3.7±1.5	16.5±9.0	---	---

AUC = area under the concertation-time curve. Tmax = time to reach the cefuroxime peak concentration. *Elimination half-life. TBC = total body clearance. DV = distribution volume.

This tale shows that cefuroxime AUC and peak concentration are lower in the brain that in plasma, cefuroxime slowly diffuses in brain as Tmax is 3.7 hours, and cefuroxime is slowly eliminated in brain as the elimination half-life of cefuroxime is 16.5 hours.

Pharmacokinetics of cefuroxime axetil in human volunteers

James et al. [13] studied the pharmacokinetic of cefuroxime axetil in 6 healthy volunteers, aged 25 years (range, 21 to 31) (Pilot study), and in 24 healthy volunteers, aged 26 years (range, 21 to 34) (Follow-up study), and a single oral dose of 250 mg of cefuroxime axetil was administered.

Table 3. Pharmacokinetic parameters of cefuroxime axetil which have been obtained in fasting or in feeding healthy subjects following a single oral dose of 250 mg of cefuroxime axetil. Values are the mean±SEM, by James et al. [13].

Dose (mg)	Subject fed	Peak conc. (µg/ml)	Tmax (h)	AUC (µg*h/ml)	§half-life
Pilot study (N = 6)					
250	No	4.19±0.30*	1.38±0.14*	12.66±0.67*	1.39±0.13
250	Yes	4.63±0.14	2.33±0.21	16.80±1.33	1.08±0.05
Follow-up study (N = 24)					
250	Yes	4.29±0.19	2.26±0.12	14.21±0.45	1.09±022

Tmax = time to reach the peak concentration. AUC = area

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under the concentration-time curve. §Elimination half-life. *P-value < 0.05 (Student t test).

This table shows that cefuroxime axetil is rapidly eliminated as the elimination half-life is about 1 hour, cefuroxime axetil Tmax is longer in feeding than in fasting subjects, AUC value of cefuroxime axetil is higher in feeding than in fasting subjects and cefuroxime axetil peak concentration is higher in feeding than fasting subjects. Thus food interferes with the gastrointestinal absorption of cefuroxime axetil.

Donn et al. [14] studied the effect of cefuroxime axetil formulation on the pharmacokinetics of cefuroxime axetil. The following formulations of cefuroxime axetil were evaluated: (1) cefuroxime axetil suspension and (2) cefuroxime axetil tablets. Twenty-four healthy male volunteers received 250 mg of cefuroxime axetil as suspension or as tablets and cefuroxime axetil was administered for 7 consecutive days.

Table 4. Pharmacokinetic parameters of cefuroxime axetil which have been obtained following 250 mg of cefuroxime axetil suspension or tablets to 24 healthy male volunteers and the treatment lasted for 7 days. Values are the mean±SD and 90% confidence intervals, by Donn et al. [14].

Parameter	Suspension	Tablets	90% Confidence intervals
Peak concentration (µg/ml)	2.21±0.35*	3.83±0.87	48.3 to 67.1
Tmax (h)	3.38±1.33*	2.48±0.97	112 to 161
$AUC_{0-\infty}$ (µg*h/ml)	11.29±1.82*	12.69±1.97	82.8 to 95.1
Elimination half-life (h)	2.04±0.87*	1.36±0.33	125 to 175
Urinary recovery (mg)			
36 to 48 hours	86.7	90.9	83.9 to 107
48 to 60 hours	72.4*	91.6	64.1 to 96.2
60 to 72 hours	88.8	82.6	64.5 to 102
72 to 84 hours	81.9*	110	65.3 to 82.0

Tmax = time to reach the peak concentration. AUC = area under the concentration-time curve. *P-value < 0.05 (ANOVA).

This table shows that all pharmacokinetic parameters of cefuroxime axetil are different according to the two formulations of cefuroxime axetil and cefuroxime axetil is recovered in the urine in significant amounts. Cefuroxime axetil is cleared from the body by hydroxylation to cefuroxime and by elimination with the urine.

Prophylaxis with cefuroxime

Intraoperative cefuroxime prophylaxis decreases the rate of postoperative infections [15]. Prophylaxis with cefuroxime, administered at the time of surgery, significantly reduced the risk for developing endophthalmitis after cataract surgery [16]. Prophylaxis with cefuroxime is associated with a low incidence of postoperative wound infection and is well tolerated in patients undergoing clean neurosurgery [17]. A single oral dose of lomefloxacin was efficacious and safe as a single intravenous dose of cefuroxime for prevention of postoperative urinary-tract infection in patients undergoing transurethral surgery [18]. Prophylaxis with cefuroxime is similar to that with cefamandole or cefazolin in prevention infections during open heart surgery [19]. Prophylaxis with cefuroximeprevents infection in patients undergoing coronary bypass surgery as that with ceftriaxone [20]. Ampicillin/sulbactam was safe and effective as cefuroxime for the prevention of infections following Caesarean delivery [21]. Prophylaxis with cefuroxime prevented infection during vascular surgery more effective than that with cefazolin [22]. Prophylaxis with cefuroxime is effective and safe for the prevention of infection in patients undergoing vascular surgery [23]. Prophylaxis with oral cefadroxil is effective as intravenously cefuroxime in the prevention of infections during trochanteric hip fracture surgery [24].

Treatment of bacterial infection with cefuroxime axetil

Treatment with oral cefuroxime axetil successfully treated community-acquired pneumonia in paediatric patients [25]. Cefuroxime axetil is an effective treatment of community-acquired pneumonia in adult patients [26]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily for 5 days, isan effective treatment of acute bronchitis [27]. Cefuroxime axetil

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effectively treats respiratory-tract infections due to Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella, or Enterobacter [28]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, effectively treated skin infections [29]. Cefuroxime axetil treated children with acute otitis media[30]. Cefdinir is treated acute exacerbation of chronic bronchitis as cefuroxime axetil [31]. Cefuroxime axetil, administered at a dose of 500 mg twice-daily is effective as amoxicillin/clavulanate, administered at a dose of 500/125 mg thrice-daily, in the treatment of patients with mild to moderate community-acquired pneumonia [32].Ceftriaxone is effective as gentamicin plus cefuroxime axetil for the treatment of patients with serious systemic bacterial infections [33]. Moxifloxacin, administered at a dose of 400 mg once-daily, was effective as cefuroxime axetil, administered at a dose of 250 mg twice-daily, in treatment of patients with community-acquired acute sinusitis [34]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, is effective as amoxicillin/clavulanate, administered at a dose of 500/125 mg thrice-daily, in treatment of patients with acute bronchitis [35]. Cefuroxime axetil, administered at a dose of 500 mg thrice-daily,effectively treated bacterial infections as amoxicillin/clavulanic acid administered at a dose of 1,200/625 mg thrice-daily [36].

Trials with cefuroxime axetil

Levofloxacin was effective as cefuroxime axetil for the treatment of infections caused by Haemophilus influenzae, Streptococcus pneumoniae or Moraxella catarrhalis [37]. A single preoperative dose of cefotaxime plus metronidazole is an efficacious as a three dose regimen of cefuroxime plus metronidazole in preventing wound infection after colorectal surgery [38]. Cefuroxime axetil is a safe and effective oral antimicrobial for the treatment of pneumonia in adults [39]. A trial with cefuroxime axetil demonstrated that this drug effectively cured bacterial exacerbations of chronic bronchitis [40]. Cefuroxime, given at a dose of 500 mg twice-daily, is clinically efficacious as cefaclor, administered at a dose of 500 mg thrice-daily, in treatment of lower respiratory-tract infections [41]. A single preoperative dose of 1.5 grams of cefuroxime significantly reduces the risk of spondylodiscitis after surgery for herniated disc [42].

Penetration of cefuroxime into the cerebrospinal fluid (CSF)

Pfenninger et al. [43] investigated the penetration of cefuroxime into the CSF of 30 children, aged 3 to 12 years, with the meningitis caused by Haemophilus influenzae (N = 13), Neisseria meningitidis (N = 9), Streptococcus pneumoniae (N = 5), or by unknown aetiology (N = 3) and cefuroxime was intravenously administered at a dose of 200 mg/kg once-daily. The duration of treatment was 11.6±2.0, 10.4±1.8, 12.8±1.6, or 11.6±2.1 days in patients with meningitis caused by Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae, or by unknown aetiology, respectively, and the minimum inhibitory concentration of these organisms ranged from 0.1 to 1.0 µg/ml.

Table 5. Cefuroxime concentrations in cerebrospinal fluid (CSF) and serum and percentage penetration of cefuroxime into CSF. Values are the mean±SEM, and (range), by Pfenninger et al. [43].

		Cefuroxime concentration (µg/ml)		
Aetiology	Number of patients	CSF	Serum	CSF/serum penetration (%)
Cefuroxime concentration 24 to 48 hours after start of treatment				
H. influenzae	13	8.8±1.5 (2.7 – 18.8)	57.4±3.8 (40.4 – 86.0)	14.5±1.8 (5.5 – 26.4)
N. meningitidis	8	4.6±0.8 (1.9 – 6.8)	61.6±8.0 (34.9 – 91.9)	7.6±1.3 (3.3 – 14.3)
S. pneumoniae	5	7.9±3.1 (3.1 – 15.8)	40.8±10.0 (16.3 – 65.1)	21.9±8.2 (7.2 – 43.8)
Unknown	3	4.7±3.5 (1.1 – 11.8)	30.5±3.8 (25.5 – 38.0)	13.2±8.9 (3.9 – 31.1)
Total	30	7.0±1.0 (1.1 – 18.8)	53.3±3.6 (16.3 – 94.9)	13.4±1.8 (13.4 – 42.3)
Cefuroxime concentration at completion of treatment				
H. influenzae	13	1.9±0.3 (0.6 – 4.1)	13.9±1.2 (0.6 – 4.1)	14.6±2.8 (3.2 – 36.0)
N. meningitidis	9	1.4±0.2 (0.5 – 2.2)	19.1±2.3 (7.8 – 28.2)	8.3±2.0 (3.1 – 20.5)

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S. pneumoniae	5	1.6±0.7 (1.3 – 2.4)	25.7±4.1 (20.1 – 41.6)	6.4±0.4 (5.8 – 7.9)
Unknown	3	1.1±0.2 (0.9 – 1.2)	15.0±1.1 (13.9 – 16.0)	7.0±0.5 (6.5 – 7.5)
Total	30	1.6±0.2 (0.5 – 4.1)	17.9±1.4 (7.8 – 42.6)	10.5±1.5 (3.1 – 36.0)

This table shows that cefuroxime penetrates into the CSF in significant amounts, the cefuroxime concentration in the CSF is higher the minimum inhibitory concentration of the organisms causing the meningitis, the meningitis was cured in all children, and there is a remarkable interindividual variability in cefuroxime concentration in serum and in CSF. This variability is accounted by the wide variation in child age and diseases.

Cefuroxime was administered intravenously at a dose of 250 mg/kg daily to 6 children. Two children had the meningitis caused Salmonella meningitis and 4 children had the meningitis caused by Haemophilus influenzae type b. The mean cefuroxime concentration in CSF was 1.34±1.3 µg/ml this concentration is higher the minimum inhibitory concentration of the pathogens causing the meningitis and the meningitis was cured in all children [44]. Cefuroxime was administered intravenously at a dose of 1.5 grams 4 times-

daily to 10 adult patients with meningitis caused by Haemophilus influenzae and the mean cefuroxime concentration was 3.2 µg/kg (range, 1.0 to 7.5). This concentration is higher the minimum inhibitory concentration of Haemophilus influenzae and the meningitis was cured in all patients [45].

Treatment of bacterial meningitis with cefuroxime

One-hundred-six children with bacterial meningitis received either ceftriaxone administered intravenously at a dose of 100 mg/kg daily (N = 53) or cefuroxime administered intravenously at a dose 240 mg/kg daily (N = 53).Ceftriaxone is superior to cefuroxime for the treatment of acute bacterial meningitis and more rapidly sterilized the cerebrospinal fluid [46]. One-hundred-seventy-four infants and children with bacterial meningitis received ceftriaxone and 159 children with bacterial meningitis received cefuroxime. At 6 week and 1 year follow-up examinationsthe incidence of hearing impairment in one or both ears was higher in the cefuroxime (18%) than in the ceftriaxone (11%) treatment group but both regimens treated the bacterial meningitis [47]. Forty-eight infants and children with bacterial meningitis received cefuroxime intravenously at a dose ranging from 90 to 300 daily mg/kg during the first 2 to 4 days of treatment and 45 to 149 mg/kg daily during the subsequent 6 to 8 days of treatment. All strains of Streptococcus pneumoniae, Neisseria meningitidis, and Salmonella typhi causing the meningitis were eradicated from the cerebrospinal fluid [48]. Three children were suffering from meningitis due to Haemophilus influenzae group b (β-lactamase-producing) and received cefuroxime intravenously at a dose of 100 mg/kg daily. The minimum inhibitory concentration of cefuroxime ranged from 0.12 to 0.5 µg/ml and the cerebrospinal fluid was sterilized after 48 hours of treatment [49].

Resistance of bacteria to cefuroxime

A total of 78 Streptococcus aureus isolates were obtained from 150 specimens of nasal specimens and the isolates showed an overall 100% resistance to ceftazidime and cefuroxime [50]. Fourteen clinical non-extended-spectrum β-lactamase isolates of Escherichia coli were isolated from the urine and the resistance was due to efflux of cefuroxime from the Escherichia coli [51]. Klebsiella pneumonia extended-spectrum β-lactamases strains were isolated from the urine of 14 patients and the resistance was caused by an increase of the minimum inhibitory concentration of this organism [52]. Ten cefuroxime-non-susceptible Klebsiella pneumoniae strains were isolated from blood cultures.The multidrug-resistant phenotype of Klebsiella pneumoniae is associated with increased acrA and ramA transcription genes and decreased ompK35 transcriptiongene [53].

Transfer of cefuroxime across the human placenta

Holt et al. [54] measured the concentration of cefuroxime in 39 maternal and umbilical venous cord serum specimens and cefuroxime was administered intravenously at a dose of 750 (N = 26) or 1.5 grams (N = 13) before delivery. Pregnant women weighted 71.5 kg (range, 56 to 105) and had a gestational age of 38.5 weeks (range, 35 to 41).

Table 6. Cefuroxime concentration in maternal and cord venous sera after cefuroxime intravenous administration at a dose of 750 mg (group A) or 1.5 grams (group B). Values are the mean and (95% confidence intervals), by Holt et al. [54].

Group	Maternal conc. (µg/ml)	Sample time (min)	Cord conc. (µg/ml)	Sampling time (min)
A (N = 26)	14.9 (10.5 – 21.1)	65 (48.8 – 96.5)	8.8 (5.8 – 9.4)	57 (37.8 – 86.4)
B (N = 13)	51.9 (33.4 – 80.9)	37 (22.8 – 58.3)	15.8 (9.5 – 26.3)	32 (21.4 – 47.9)

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This table shows that the mean cefuroxime concentration in the umbilical venous cord serum is about one half of that in the maternal serum suggesting that cefuroxime is freely transferred across the human placenta.

Cefuroxime was administered intramuscularly at a dose of 750 mg to 12 pregnant women at term of gestation undergoing Caesarean delivery. Cefuroxime crossed the placenta well and produced effective concentrations in fetal blood and amniotic fluid [55]. The placental transfer of cefuroxime was studied in 20 women after one or more 1.5 grams intravenous injections. Ten women had labour induced at term and 10 women delivered by elective Caesarean section. High concentrations of cefuroxime were found in the umbilical cord blood and amniotic fluid and therapeutically active antibiotic levels were found in the infants for up to six hours after delivery [56].

Migration of cefuroxime into the breast-milk

A single intravenous dose of 750 mg of cefuroxime was given to 5 lactating women. The average peak cefuroxime in the breast-milk was 0.37 µg/ml. Individual peak concentrations of 0.35 to 0.5 µg/ml occurred 2 to 4 hours after dosing [57]. A single intramuscular injection of 750 mg of cefuroxime was

given to 8 lactating women and the milk concentrations increased from 0.34 µg/ml at 30 min after the injection to 1.45 µg/ml at 8 hours after the injection [58]. Two lactating women received intravenous cefuroxime at a dose of 750 mg thrice-daily for 2 days following Caesarean delivery and donated the breast-milk samples 1 hour after the dose and the milk concentration of cefuroxime was 0.34µg/ml [59]. Cefuroxime axetil was administered intravenously at a dose of 500 mg thrice-daily for 8 days to 10 lactating women with acute mastitis. Cefuroxime axetil concentrations in the breast-milk ranged from 0.09 to 0.59 µg/ml (mean: 0.32±0.25) at 30 to 90 min after dosing, respectively [60].

Discussion

Cefuroxime is a second-generation cephalosporin and is active against Haemophilus influenzae (including strains resistant to ampicillin), Neisseria meningitidis, and Streptococcus pneumoniae and the activity against Escherichia coli and Klebsiella is modest. Cefuroxime axetil is 1-acetyloxyethyl ester of cefuroxime and between 30% and 50% of cefuroxime axetil is absorbed following oral administration. The efficacy and safety of cefuroxime axetil have been reported [2-10]. Extended-release cefuroxime axetil tablets administered once-daily is safe and efficacy as cefixime tablets in the treatment of patients with acute tonsillopharyngitis [2]. Cefuroxime axetil, administered for 4 days, is as efficacy as penicillin, administered for 10 days, in the treatment of children with acute group A β-haemolytic Streptococcus pharyngitis [3], and cefuroxime axetil is efficacy and well-tolerated in children with respiratory-tract or soft-tissue infections [4]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, is efficacious as augmentin, administered at a dose of 375 mg thrice-daily, in the treatment of upper respiratory-tract infections [5]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, is efficacious as amoxicillin/clavulanate administered at a dose of 500 mg thrice-daily in treatment of acute sinusitis [6] and in the treatment of bacterial maxillary sinusitis [7]. Cefuroxime is similarly efficacious as levofloxacin in the treatment of exacerbation of chronic obstructive pulmonary disease [8], cefuroxime is efficacy and safe in the treatment of acute pyelonephritis during pregnancy [9], and ceftriaxone is efficacy and safe as ceftriaxone plus gentamicin in treating faecal flora infection [10]. The diffusion of cefuroxime into body-tissues has been assessed following the administration of 1.5 grams as bolus infusion (N = 6) or as a continuous infusion of 1.5 grams of cefuroxime (N = 6). The peak cefuroxime concentration in muscle and subcutaneous tissue is about one-third of that in plasma and the time to reach the peak is 0.17 hours in plasma and 1.1 hours in muscle and subcutaneous tissue [11]. Following intravenous administration of 1.5 grams of cefuroxime, cefuroxime peak concentration in the brain is about 10% of that in plasma and the time to reach the peak concentration is 1 hour in plasma and 3.7 hours in the brain [12]. The pharmacokinetics of cefuroxime axetil have been studied in healthy volunteers and cefuroxime axetil elimination half-life is about 1 hour [13]. The pharmacokinetics of cefuroxime axetil have been studied in healthy volunteers following the administration of cefuroxime axetil suspension or tablets. The time to react cefuroxime axetil peak concentration is 3.38 and 2.48 hours (P-value < 0.05) following the administration of cefuroxime axetil suspension and tablets, respectively. Cefuroxime axetil elimination half-life is 2.04 and 1.36 hours (P-value < 0.05) following the administration of cefuroxime axetil suspension and tablets, respectively, and cefuroxime axetil is eliminated in the urine [14]. The prophylaxis with cefuroxime has been reported [15-24]. Cefuroxime decreases the rate of postoperative infections [15], reduces the risk ofdeveloping endophthalmitis after cataract surgery [16], reduces wound infection in patients undergoing clean neurosurgery [17], and prevents postoperative urinary-tract infection in patients undergoing transurethral surgery [18]. Prophylaxis with cefuroxime is similar to that with cefamandole or cefazolin in preventing infection during heart surgery [19]. Prophylaxis with ceftriazone is effective as that with cefuroxime in patients undergoing coronary bypass surgery [20]. Prophylaxis with ampicillin/sulbactam is effective as that with cefuroxime for the prevention of infections following Caesarean delivery [21]. Prophylaxis with cefuroxime is more effective than that

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with cefazolin in preventing infections during vascular surgery [22], prophylaxis with cefuroxime prevents infection in patients undergoing vascular surgery [23], and the prophylaxis with oral cefadroxil is effective as that with intravenous cefuroxime in preventing infections in patients undergoing trochanteric hip fracture surgery [24]. The treatment of bacterial infection with cefuroxime axetil has been extensively studied [25-36].Cefuroxime axetil treats community-acquired pneumonia in paediatric patients [25] and in adult patients [26]. Cefuroxime axetil treats acute bronchitis [27], treats infections due to Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella or Enterobacter [28], treats skin infections [29], and treats acute otitis media [30]. Cefdinir treats acute exacerbation of chronic bronchitis as cefuroxime axetil [31]. Cefuroxime axetil, administered at a dose of 500 mg twice-daily, is effective as amoxicillin/clavulanate, administered at a dose of 500/125 mg thrice-daily, in treatment of community-acquired pneumonia [32]. Ceftriaxone is effective as gentamicin plus cefuroxime axetil for treatment of patients with serious systemic bacterial infections [33]. Moxifloxacin, administered at a dose of 400 mg once-daily, is effective as cefuroxime axetil, administered at a dose of 250 mg twice-daily, in treatment of patients with community-acquired acute sinusitis [34]. Cefuroxime axetil, administered at a dose of 250 mg twice-daily, is effective as amoxicillin/clavulanate, administered at a dose of 500/125 mg thrice-daily, in treatment of patients with acute bronchitis [35]. Cefuroxime axetil, administered at a dose of 500 mg thrice-daily, is effective as amoxicillin/clavulanate, administered at a dose of 1,200/625 mg thrice-daily, in treatment of bacterial infections [36]. The trials with cefuroxime axetil have been reported [37-42]. Levofloxacin is effective as cefuroxime axetil for treatment of infections caused by Haemophilus influenzae, Streptococcus pneumoniae, or Moraxella catarrhalis [37], a single preoperative dose of cefuroxime plus metronidazole is efficacious as 3 doses of cefuroxime plus metronidazole in preventing wound infection after colorectal surgery [38], cefuroxime axetil effectively treats pneumonia [39] and effectively treats bacterial exacerbations of chronic bronchitis [40].Cefuroxime, given at a dose of 500 mg twice-daily, is efficacy as cefaclor, administered at a dose of 500 mg thrice-daily, in treatment of lower respiratory-tract infections [41], and a single preoperative dose of 1.5 grams of cefuroxime reduces the risk of spondylodiscitis after surgery of herniated disk [42]. The penetration of cefuroxime into the cerebrospinal fluid has been reported in 3 studies [43-45]. Following the intravenous administration of cefuroxime at a dose of 200 mg/kg once-daily to 30 children, the cefuroxime concentration in the cerebrospinal fluid ranges from 1.1 to 8.8 µg/ml and this concentration is higher the minimum inhibitory concentration of Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae which were the organisms causing the meningitis and the meningitis was cured in all children [43]. Cefuroxime was administered intravenously at a dose of 250 mg/kg daily to 6 children with the meningitis caused by Salmonella meningitis (N = 4) or by Haemophilus influenzae type b (N = 2) and the mean cefuroxime concentration in the cerebrospinal fluid is 1.3 µg/ml. This concentration is higher the minimum inhibitory concentration of the pathogens causing the meningitis and the meningitis was cured in all children [44]. Cefuroxime was administered intravenously at a dose of 1.5 grams 4 times-daily to 10 adult patients with the meningitis caused by Haemophilus influenzae, the mean cefuroxime concentration in the cerebrospinal fluid is 3.2 µg/ml, this concentration is higher than the minimum inhibitory concentration of Haemophilus influenzae, and the meningitis was cured in all patients [45]. The treatment of bacterial meningitis with cefuroxime is reported in 4 studies [46-49]. Fifty-three children with bacterial meningitis received 100 mg/kg daily of ceftriazone intravenously and 53 children received 240 mg/kg daily cefuroxime intravenously and the cerebrospinal fluid was sterilized with both regimens [46]. One-hundred-seventy-four infants and children with bacterial meningitis received ceftriazone and 159 infants and children with bacterial meningitis received cefuroxime. The hearing impairment occurred in 18% of patients treated with cefuroxime and in 11% of patients treated with ceftriaxone and the meningitis was cured in all patients [47]. Forty-eight infants and children with bacterial meningitis received cefuroxime intravenously at a dose of 90 to 300 mg/kg daily during the first 2 to 4 days of treatment and 45 to 149 mg/kg daily during the subsequent 6 to 8 days of treatment. The meningitis was caused by Streptococcus pneumoniae, Neisseria meningitidis, or by Salmonella typhi and the treatment eradicated these pathogens from the cerebrospinal fluid [48]. Three children with the meningitis caused by Haemophilus influenzae type b (β-lactamase-producing) were treated with cefuroxime intravenously at a dose of 100 mg/kg daily and the cerebrospinal fluid was sterilized [49].Some bacteria may become resistant to cefuroxime [50-53]. Streptococcus aureus was resistant to ceftazidime and cefuroxime [50], the resistance in Escherichia coli is due to efflux of cefuroxime from this organism [51], the resistance of Klebsiella pneumoniae is caused by an increase of the minimum inhibitory concentration of this organism [52], and the resistance of Klebsiella pneumoniae is associated with increased acrA and ramA transcription genes and decreased ompK35 transcription gene [53]. The transfer of cefuroxime across the human placenta has been described in three studies [54-56] and cefuroxime freely crosses the human placenta. The migration of cefuroxime into the breast-milk has been

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reported in 4 studies [57-60] and the concentration of cefuroxime in the beast-milk is usually less than 1 µg/ml suggesting that cefuroxime poorly migrates into the breast-milk.

In conclusion, cefuroxime is a second-generation and is active against Haemophilus influenzae (including strains resistant to ampicillin), Neisseria meningitidis, and Streptococcus pneumoniae and the activity against Escherichia coli and Klebsiella is modest. The efficacy and safety of cefuroxime axetil has been extensively studied and cefuroxime diffuses into muscle and subcutaneous tissue in significant amounts and cefuroxime peak concentration in brain is about 10% of that in plasma. The pharmacokinetics of cefuroxime axetil have been studied in healthy volunteers, cefuroxime axetil elimination half-life is about 1 hour and cefuroxime axetil is eliminated in the urine. The prophylaxis, treatment, and trials with cefuroxime axetil have been extensively studied. Cefuroxime penetrates into the cerebrospinal fluid in significant amounts and cefuroxime treats bacterial meningitis. Cefuroxime may become resistant to bacteria, is freely transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of cefuroxime.

Conflict of interests

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

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

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