

A Review on pharmacokinetic properties & therapeutic efficacy of Cefuroxime axetil

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1. Abstract: Cefuroxime axetil is a second generation oral cephalosporin antibiotics. It was discovered by Glaxo & approved by FDA on December 28, 1987(7). It is sold under the name ceftin among others. Cephalosporin work as a bactericidal antibiotic that by binding to penicillin binding proteins & inhibit the last step of the bacterial cell wall & leakage. Cefuroxime axetil is given with food, absorption values can increased by 52% compared to fasting patient. It is distributed in body fluids & tissue. It is highly effective against many of respiratory pathogens. They generally use in obstetrics, gynecological infection, urinary tract infection, skin & soft tissue infection, uncomplicated gonorrhea & it is safe to use in pregnancy.

2. Introduction :

Cefuroxime is a semisynthetic, broad-spectrum second-generation cephalosporin antibiotics. It was discovered by Glaxo & introduced in 1987(6). It was approved by FDA on 28 December 1987 & available by GSK as ceftin in US (8) & ceftum in india(9). This antibiotics treat only the bacterial infection. Cefuroxime axetil has essentially the same antibacterial activity as its parent moiety, making cefuroxime the only the second generation cephalosporin with both an intravenous & oral formulation(1).

3. Antibacterial Activity :

Cefuroxime axetil sold under the brand name Ceftin among other. It is second generation cephalosporin antibiotics. The drug shows good activity against a broad range of Gram-positive and Gram-negative bacteria in vitro(27), including those most commonly associated with respiratory tract infections [e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *S. pyogenes* and methicillin-sensitive *Staphylococcus aureus* (MSSA)](29).

3.1 Gram-positive bacteria :

Cefuroxime was active against methicillin sensitive and oxacillin-sensitive strains of *Staphylococcus aureus* and *S. epidermidis*. The activity of cefuroxime against *S. aureus* was superior to that of cefaclor and was broadly similar to that of amoxicillin/clavulanic acid & cefadroxil. Against oxacillin-sensitive strains of *S. epidermidis* and *S. aureus* cefuroxime was more active than the third generation cephalosporin cefixime(29).

Cefuroxime, like most other beta lactam antibiotics, has little or no activity against methicillin resistant strains of *Staphylococcus* species (including methicillin-resistant *S. aureus*). Cefuroxime is also inactive against enterococci and *Listeria monocytogenes*(2).

A study that investigated the susceptibility of penicillin-susceptible, -intermediate and -resistant pneumococci to cefuroxime reported that cefuroxime was active against penicillin-susceptible strains of *S. pneumoniae*, with an MIC₉₀ of 0.125 mg/L(10). However, cefuroxime was less active against penicillin-intermediate strains of *S. pneumoniae* (MIC₉₀ 2.0 mg/L), and most penicillin resistant strains of *S. pneumoniae* were resistant to the drug.

3.2 Gram-Negative bacteria :

Cefuroxime has good activity against *H. influenzae* & MIC₉₀ value are similar for for beta lactamase positive & negative strain(3). Cefuroxime had broadly similar activity to amoxicillin/ clavulanic acid & ciprofloxacin against *H. influenzae*, & was more active than cefaclor against both beta lactamase positive & negative strains(12).

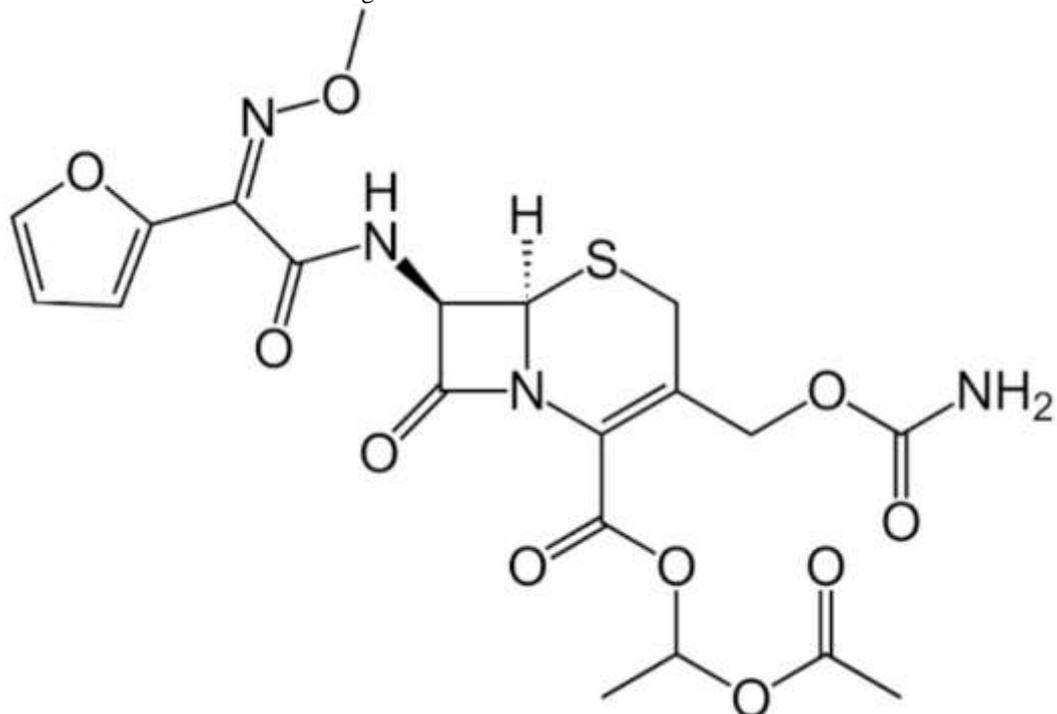
Cefuroxime, amoxicillin/clavulanic acid and cefaclor MIC₉₀ and MIC₅₀ (minimum inhibitory concentrations required to inhibit 50% of strains) values reported for *H. influenzae*, *M. catarrhalis* and penicillin sensitive isolates of *S. pneumoniae*.

4. Chemistry :

Cefuroxime axetil is Chemically designated as 1-Acetoxyethyl (6*R*,7*R*)-3-[(carbamoxyloxy)methyl]-7-[[{(2*Z*)-2-(2-furyl)-2-(methoxyimino)acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Cefuroxime axetil is a white crystalline powder. It is soluble in acetone, sparingly soluble in chloroform, ethyl acetate, methanol; slightly soluble in dehydrated alcohol. Insoluble in ether & water.

Fig : Structure of cefuroxime axetil



Properties	Description
Chemical Name	1-Acetoxyethyl (6R,7R)-3-[(carbamoyloxy)methyl]-7-[(2Z)-2-(2-furyl)-2-(methoxyimino)acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.
Brand Name	Ceftin, ceftum, zinnat
Formula	$C_{20}H_{22}N_4O_{10}S$
Molar mass	510.475g/mol
CAS Registry No.	64544-07-6
Melting point	204-206° C
UV Spectrum	λ max 282 nm
Refractive index	1.665
Storage	Store in cool & dry place
Density	1.61g/cm ³

5. Mechanism of action :

Cefuroxime axetil is a second generation cephalosporin that, like penicillins antibiotics, contains a beta lactam ring structure. Cephalosporins works as a bactericidal antibiotic that binding to penicillin-binding protein (PBPs), inhibit the last step of bacterial cell wall synthesis(4). Once the beta lactam ring bind to PBPs, cross-linking between peptidoglycan unit is inhibited(3).

6. Pharmacokinetic Properties :

The pharmacokinetics of cefuroxime after administration of oral cefuroxime axetil have been studied extensively in healthy adult volunteers and in patients infected with organisms susceptible to cefuroxime(16). These studies have been reviewed previously in Drugs and elsewhere and a brief overview is presented here. cefuroxime sodium is a parent molecule they poorly absorbed after the oral administration. In contrast, the lipophilic acetoxyethyl-ester prodrug cefuroxime axetil is rapidly hydrolysed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime and the ester group & they well absorbed from the gastrointestinal tract. Cefuroxime axetil is available in tablet and a suspension form. Whereas the tablet form releases the drug into the stomach(17), the suspension releases cefuroxime axetil into the upper small intestine. This gives rise to differences in bioavailability and the time-concentration curve. The pharmacokinetic properties of cefuroxime axetil following administration of the different formulations to adults and children.

Table I. Mean pharmacokinetic parameters of cefuroxime after oral administration of cefuroxime axetil (tablet or suspension formulations) to healthy adult volunteers, children with infections, healthy elderly volunteers or elderly patients

Dose	C max (mg/L)	tmax (h)	AUC _∞ (mg/L • h)	t1/2 (h)
After administration of tablets immediately after a meal to 12 healthy adult volunteers				
125 mg	2.1	2.2	6.7	1.2
250 mg	4.1	2.5	12.6	1.2
500 mg	7.0	3.0	25.8	1.2
1000mg	13.2	2.5	50.1	1.3
After administration of oral suspension to paediatric patients (mean age 23 months) with infections				
10 mg/kg	3.3	3.6	12.4b	1.4
14 mg/kg	5.1	2.7	22.5b	1.9
20 mg/kg	7.1	3.1	32.8b	1.9
After administration of oral suspensions of different concentrations to 18 healthy adult volunteers (with food)				
250mg/5ml	2.2	3.0	8.9b	1.4
2 × 125 mg/5ml	2.4	3.0	9.8b	1.4
After administration of tablets to 10 elderly patients (mean age 78.6 years) for 5 days				
250mg q 12h(day1)	10.3	2.8	59.4	2.4
250mg q 12h(day5)	11.3	3.1	60.6	2.3
After administration of oral suspension to 12 healthy elderly volunteers (mean age 71 years)				
250 mg	3.38	3.0(median)	15.7	1.9

a Single dose values unless stated otherwise.

b Time period not reported.

AUC_∞ = area

under the plasma concentration-time curve from zero to infinity; **C_{max}** = peak plasma concentration; **q12h** = every 12 hours; **t1/2**

= elimination half-life; **t_{max}** = time to C_{max}

6.1 Absorption :

In a study which compared oral cefuroxime axetil and intravenous cefuroxime administered after food(10), the mean absolute bioavailability of cefuroxime was 67.9% (n = 12). The extent bioavailability of absorption of cefuroxime is increased by coadministration of cefuroxime axetil with meal. In a 6-way randomised crossover study in 12 healthy male volunteers, administration of a 500mg dose of cefuroxime axetil with food increased the extent of absorption from 36% (fasting individuals) to

52%, and the peak plasma concentration (C_{max}) was 43% greater. The pharmacokinetic profile of cefuroxime axetil (immediately administered after meal) is linear over the 125 to 1000mg dose range. The peak plasma concentration (C_{max}) ranged from 2.1 to 13.6 mg/L over this dose range while the corresponding values for elimination half-life (t_{1/2}), time to C_{max} and time-curve (AUC) area under the plasma concentration were 2.2 to 3 hours, 1.2 to 1.3 hours and 6.7 to 50 mg/L • h, respectively, when the drug was administered as an oral tablet(16). As mentioned, Cefuroxime axetil are different pharmacokinetics of the tablet & suspension are administered after food. and they have been compared in a crossover study in 12 healthy volunteers. After ingestion of 250mg cefuroxime axetil in either tablet or suspension form following a meal, there was little difference in the elimination half-life (t_{1/2}) or time to C_{max} (t_{max}); however, both the area under the plasma concentration-time (AUC) curve and C_{max} were significantly lower after ingestion of the suspension than after the tablet. The C_{max} of cefuroxime was 4.04 and 2.48 mg/L for the tablet and suspension, respectively, whereas the corresponding AUC values were 14.02 and 10.22 mg/L • h (p = 0.001 for both comparisons)(12).

6.2 Distribution :

After oral cefuroxime axetil protein binding has not been studied but in the case of plasma protein binding of cefuroxime after intravenous injection of cefuroxime has been reported as 33%, whereas the manufacturer's prescribing information reports a binding level of 50%. They has a relatively very small volume of distribution of 0.25 to 0.3 L/kg. The distribution of cefuroxime into fluids & body tissues within 5 hours of administration is summarised in table II. The highest levels of penetration of cefuroxime axetil (single dose of 375 or 500mg) were seen in sinus tissue (38.1 to 106% with tissue concentrations of 0.4 to 2.4 mg/kg). Penetration into bronchial mucosa and tonsil tissue was also good (35 to 90%) In addition, after administration of a single dose of cefuroxime axetil 250mg. Mean tissue concentrations in these patients were 1.2 and 1.3 mg/kg and in 1 of these studies 29.8% tissue penetration. Penetration into aqueous humor was relatively low at 13.8%, but the mean cefuroxime concentration obtained (0.5 mg/L) was below the MIC₉₀ for most, but not all, of the organisms frequently involved in intraocular infections(16).

6.3 Elimination :

Cefuroxime is released from cefuroxime axetil by de-esterification, but is not metabolised further and approximately 50% of the drug is eliminated unchanged in the urine within 12 hours(10). In healthy adult volunteers who received a single oral dose of cefuroxime axetil 250mg, urinary recovery ranged from 42.8 to 57% in this time period. The t_{1/2} in adult volunteers who received the tablet formulation was 1.2 to 1.3 hours and those who received the oral suspension of cefuroxime axetil was 1.4 hours. Because cefuroxime is eliminated renally the t_{1/2} increases with decreasing renal function. In the Japanese study evaluated pharmacokinetics of cefuroxime after administration of cefuroxime axetil 500mg in healthy volunteers or otherwise healthy individuals with varying degrees of renal impairment. The t_{1/2} was 1.4, 2.4, 4.6 and 16.8 hours in patients with creatinine clearance of >85, 50 to 84, 15 to 49 and < 10 ml/min respectively.

Table II. Concentrations of cefuroxime and degree of penetration after administration of oral cefuroxime axetil in various tissues and fluids in adult and paediatric patients with bacterial infections

Tissue or body fluid	Single dose (mg)	Mean tissue or fluid concentration (mg/L or mg/kg)	Mean tissue or fluid penetrationa (%) 0 to 5h after administration
Alveolar macrophages	500	1.8	NR
Epithelial lining fluid			
Bronchial secretions	500	0.7	NR
Bronchial secretions			
Bronchial mucosa	500b	NR	12
Bronchial mucosa			
Tonsil tissue	500b	2.3-3.3	30
Sinus tissue	500	3.8	44-90
Sinus tissue			
Sinus tissue	500	2.2	43.3
Sinus tissue	500	3.8	35
Middle ear effusion	500	1.4	80
Middle ear effusion	500	1.2(median)	77(median)
Aqueous humor	375b	0.4	38.1
Interstitial fluid	500b	2.4	106
Bone	250	1.2	Nr
Joint fluid			
	15 mg/kg	1.3	29.8
	500	0.5	13.8

Tissue or body fluid	Single dose (mg)	Mean tissue or fluid concentration (mg/L or mg/kg)	Mean tissue or fluid penetration (%) 0 to 5h after administration
	250	1.1	NR
	500-1000b	1.0	23-30
	500-1000b	2.3	38-42

a Expressed as a ratio of concentration of cefuroxime in tissue/fluid versus concentration in serum.

b Study participants received multiple doses of cefuroxime axetil.

c Skin-window technique used.

NR = not reported

7. Therapeutic Efficacy :

Numerous clinical trials have investigated the therapeutic efficacy of cefuroxime axetil in patients with community-acquired upper respiratory tract infections (pharyngitis, tonsillitis, tonsillopharyngitis, otitis media and sinusitis), lower respiratory tract infections (chronic bronchitis, acute exacerbations of chronic bronchitis and community-acquired pneumonia), urinary tract infections, skin and soft tissue infections, gonorrhoea and early stage Lyme disease(12).

Cefuroxime axetil 250 or 500mg twice daily was administered orally for up to 14 days, although intravenous (cefuroxime) /oral (cefuroxime axetil) sequential therapy was selected for some patients, in particular, those with CAP.

7.1 Respiratory tract infections :

250 to 500 mg cefuroxime axetil used for most study protocols in twice daily. The majority of clinical studies were randomised, comparative and nonblind or single blind in design. Causative pathogens were identified prior to treatment initiation and patients with infections caused by pathogens resistant to cefuroxime were excluded from study participation(27). Cefuroxime axetil was investigated as empirical treatment for unspecified respiratory tract infections in a small number of studies. Most clinical investigations were conducted by hospital clinicians in the outpatient setting. In most studies, different numbers of patients were evaluable for clinical and bacteriological assessments(2).

Upper respiratory tract infections :

In upper respiratory tract infection the most common causative pathogen *S. pyogenes* [group A haemolytic streptococcus (GABHS)], *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Less frequently, *S. aureus* and some anaerobic bacteria were identified(3).

The bacteriological & clinical efficacy of cefuroxime axetil in URTIs has been demonstrated in several previously reviewed comparative randomised trials. In these trials, treatment with cefuroxime axetil was effective at least 10 to 14 days, treatment with phenoxymethylpenicillin (penicillin V) in achieving clinical cure and bacterial eradication in children, adults & adolescents with group A β -haemolytic streptococcal (GABHS) tonsillopharyngitis, tonsillitis or pharyngitis. Notably, in 3 studies in patients with GABHS, clinical cure rates and bacterial responses were significantly higher with 10 days' cefuroxime axetil than 10 days' phenoxymethylpenicillin. Additionally, in children and adults with acute otitis media(19), overall response rates (cure or improvement) with cefuroxime axetil (70 to 100% of patients) were similar to those obtained with amoxicillin/clavulanic acid, amoxicillin, cefotiam hexetil and cefaclor. Similarly, consistently high response rates (79 to 100% of patients) were achieved in adults with acute sinusitis and acute exacerbations of chronic sinusitis(19). These response rates were similar to those of amoxicillin/clavulanic acid, cefaclor, cefixime and cefpodoxime proxetil(13).

Lower respiratory tract infections :

As reviewed previously, cefuroxime axetil (250 to 500mg twice daily for 5 to 10 days) was at least as effective as amoxicillin/clavulanic acid, and similar to cefaclor or cefpodoxime proxetil in the treatment of patients with LRTIs, with >72% of patients achieving clinical responses (cure or improvement) with cefuroxime axetil treatment. Furthermore, cefuroxime axetil 5 days course was shown to be as effective as a 10-day course of either cefuroxime axetil or amoxicillin/ clavulanic acid in patients with secondary bacterial infections of acute bronchitis. In the sequential therapy (intravenous cefuroxime administered for 2 to 3 days then changed to oral cefuroxime axetil for the remainder of the course of treatment) was effective in the treatment of CAP or AECB (clinical cure or improvement achieved by $\geq 80\%$ of patients at the end of treatment), showing comparable efficacy to amoxicillin/clavulanic acid sequential therapy or full parenteral courses of cefuroxime, cefotiam or cefoperazone(13-28).

7.2 Urinary Tract Infections :

The comparative studies that evaluated the efficacy of cefuroxime axetil in patients with urinary tract infections were conducted in the hospital outpatient setting and included adults with acute uncomplicated urinary tract infections(22). The most commonly identified causative pathogens were *E. coli*, *K. pneumoniae* and *P. mirabilis*.

In earlier studies, single-dose (1000mg), short-term (150.36mg twice daily for 3 days) or 7 to 10 days' treatment (250 to 500 mg/day) with cefuroxime axetil demonstrated clinical and bacteriological efficacy in adult patients with complicated or

uncomplicated UTIs. In these trials, cefuroxime axetil was at least as effective as cefaclor, cephradine, cefalexin, ofloxacin or cefetamet pivoxil.

7.3 Skin and Soft Tissue Infections :

The most common pathogens responsible for community-acquired primary and secondary skin infections are *S. aureus* and *S. pyogenes*, the majority of which are p-lactamase positive staphylococci resistant to phenoxymethylpenicillin(24). Clinical cure or improvement was reported in >90% of adults with mild to moderate skin and skin structure infections (culture-positive pyoderma, impetigo, furunculosis, cellulitis, carbuncles, folliculitis or infected wounds) after 10 days' treatment with cefuroxime axetil 250 to 500mg twice a day(25). Cefuroxime axetil was as effective in achieving clinical cure or improvement as cefaclor and cefadroxil and was significantly more effective than cefalexin ($p = 0.04$).

7.4 Gonorrhoea :

Cefuroxime is active against *N. gonorrhoeae*, including beta-lactamase producing strains. Studies evaluating the therapeutic efficacy of cefuroxime axetil in men and women with culture-proven uncomplicated symptomatic and asymptomatic gonococcal genitourinary, pharyngeal or rectal infections have been conducted in the US, Canada and Europe. Cure was generally defined as elimination of gonococci assessed by culture and microscopy(21).

Cefuroxime axetil, administered as a single 1 to 1.5g dose either alone or in combination with a single oral 1g dose of probenecid, produced cure rates of 96 to 100% in patients with genitoretal gonococcal infections(23).

7.5 Lyme Disease :

Lyme disease (Lyme borreliosis), a systemic illness caused by the tick-borne bacterium *Borrelia burgdorferi*, is the most common arthropod transmitted disease reported in the US. A characteristic expanding skin lesion (erythema migrans) accompanied by flu- or meningitis-like symptoms is the early clinical manifestation of this disease and provides the best clinical marker for identifying infected patients(3). Traditionally, phenoxymethylpenicillin or tetracycline have been the drugs of choice for the management of Lyme disease; however, amoxicillin and doxycycline are being increasingly used. cefuroxime axetil demonstrates similar activity to doxycycline against *B. burgdorferi*, 3 multicentre clinical studies ($n = 436$) compared the therapeutic efficacy of cefuroxime axetil with doxycycline in patients with early Lyme disease associated with erythema migrans(2).

8. Conclusion :

Cefuroxime axetil is a bactericidal agent. It inhibit bacterial cell wall & stopping the growth of bacteria. Cefuroxime axetil is safe to use in pregnancy. It has a low adverse effect profile but its better therapeutic alternatives.

9. Acknowledgment :

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