

Cefuroxime Axetil (Ceftin®): A Brief Review

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KEY WORDS

cefuroxime axetil; antimicrobial; uncomplicated gonorrhea

Cefuroxime axetil (Ceftin®, Glaxo Wellcome, Research Triangle Park, NC) is the oral pro-drug formulation of the injectable antibiotic cefuroxime sodium. It has essentially the same antibacterial activity as its parent moiety, making cefuroxime the only second-generation cephalosporin with both an intravenous and oral formulation.

STRUCTURE AND DERIVATION

Cefuroxime axetil is the 1-acetoxyethyl ester of cefuroxime. The axetil salt renders the molecule more lipophilic, thus allowing enhanced oral absorption.¹ Once cefuroxime axetil reaches the intestinal mucosa and portal blood flow it rapidly undergoes de-esterification to yield the active parent compound cefuroxime.¹

MECHANISM OF ACTION

Cefuroxime axetil is a second-generation cephalosporin that contains the classic β -lactam ring structure. Bactericidal activity in vivo is resultant of its binding to essential target proteins, termed the penicillin-binding proteins, which are located in the bacterial cell wall. Inhibition of these proteins leads to bacterial cell wall elongation and leakage, thus the bacteria are unable to divide and mature.²

PHARMACOKINETICS

Cefuroxime axetil is available as a tablet and a flavored suspension. Although the tablets have undergone three product reformulations in an attempt to standardize absorption, the bioavailability issues have been resolved with the currently marketed

tablet. Cefuroxime axetil is converted to the active moiety, cefuroxime, in less than 3 min once absorbed.¹ Due to the rapid conversion it is not possible to detect cefuroxime axetil in the systemic circulation.¹ Peak serum concentration achieved after a single 250 mg dose in the fed state is 4.7 mcg/ml and is reached after 2.1 h post-ingestion.³ The administration of food with cefuroxime axetil substantially increases its absorption.^{1,4,5} The bioavailability was shown to increase from 36% to 52% when a 500 mg dose was taken in a fasting state compared to being administered after food.⁵ The mechanism for this increased bioavailability is not completely understood. It has been proposed that food-induced cholecystokinin release which causes the gall bladder to contract and release bile may be responsible for improving absorption.⁶

Cefuroxime axetil, as cefuroxime, is approximately 30% protein bound and has a volume of distribution of about 17 l.⁷ Distribution of this antibiotic into body fluids and tissues is variable, however, it does penetrate well (35–90%) into the tonsil tissue, sinus tissue, and bronchial mucosa.⁸

Once de-esterified and released into systemic circulation, cefuroxime is not metabolized further, but is eliminated unchanged in the urine. In patients with normal renal function, the plasma elimination half-life after a dose of 500 mg of cefuroxime is 1.4 h. The elimination half-life increases as the renal function declines. In patients with creatinine clearances <10 ml/min the elimination half-life extends to approximately 16.8 h.⁹ Based on these results, it is recommended that the dosing interval be

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TABLE 1. Dosage guidelines for renal dysfunction^a

Estimated creatinine clearance	Recommended dosage
30–49 ml/min/1.73 m ²	Standard individual dose given every 12 h
10–29 ml/min/1.73 m ²	Standard individual dose given every 24 h
<10 ml/min/1.73 m ²	Standard individual dose given every 48 h

^aAdapted from Konishi et al.⁹

extended in patients with renal dysfunction (see Table 1).

SIDE EFFECTS AND INTERACTIONS

Cefuroxime axetil is associated with a low incidence of adverse effects and is generally well tolerated. The most frequently reported adverse effects are primarily gastrointestinal in nature, including diarrhea/loose stools (3.7%), nausea (2.6%), and vomiting (2.6%).^{10,11} In clinical trials comprised of large cohorts of patients (n = 912) using multiple doses of cefuroxime axetil, only 2.2% of patients discontinued treatment due to adverse reactions. Of those who discontinued treatment, 85% did so because of gastrointestinal complaints.¹⁰

Other occasionally reported adverse events associated with cefuroxime axetil include antibiotic-associated colitis and liver function abnormalities. Hypersensitivity reactions including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported rarely during post-marketing surveillance.^{10,11}

Concurrent use of cefuroxime with probenecid may increase the serum concentration of cefuroxime. Use with warfarin may increase the hypoprothrombotic effect of the anticoagulant; therefore, closer monitoring of the patient's international normalized ratio during cefuroxime therapy is recommended.¹⁰

SPECTRUM OF ANTIMICROBIAL ACTIVITY

Cefuroxime axetil has a wide spectrum of bactericidal activity both in vivo and in vitro against many gram-positive bacteria, some gram-negative bacteria, and few anaerobic bacteria. It even covers those strains that produce β -lactamases.¹² It is highly effective against many of the common respiratory pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It is

one of the few oral cephalosporins with some activity against isolates of *S. pneumoniae* that are intermediately resistant to penicillin.¹³ It also has good activity against the pathogens that lead to skin and soft tissue infections, including methicillin-sensitive staphylococci and *S. pyogenes*. The most frequently encountered urinary tract infection pathogens, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*, are also susceptible to cefuroxime axetil. Cefuroxime axetil has coverage for both the penicillinase-positive and -negative strains of *Neisseria gonorrhea*, and thus is an alternative choice for uncomplicated gonorrhea. It has activity against *Borrelia burgdorferi*, the bacteria responsible for Lyme disease, and some anaerobic bacteria such as *Peptococcus* species. Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant, and therefore render this antibiotic a poor choice for most obstetric and gynecological surgeries.^{10,14}

Pseudomonas species, *Campylobacter* species, *Acinetobacter calcoaceticus*, most strains of *Serratia* species, *Proteus vulgaris*, and certain strains of *Enterococci* are resistant to therapy with cefuroxime axetil.¹⁰ Resistance is being reported for some nosocomial isolates of Enterobacteriaceae, primarily *K. pneumoniae* and *E. coli*. This is due to bacterial production of novel plasmid-mediated β -lactamases.¹⁵

CLINICAL APPLICATIONS

Multiple clinical trials have investigated the therapeutic efficacy of cefuroxime axetil in upper and lower respiratory tract infections, uncomplicated urinary tract infections, skin and soft tissue infections, uncomplicated gonorrhea, and early stage Lyme disease. Although cefuroxime axetil has labeled indications for all of the previously mentioned infections,¹⁰ it is generally not the preferred antibiotic for initial treatment since equally efficacious and less expensive options are available. For general use in obstetrics and gynecological infections, cefuroxime axetil may be considered a useful alternative for treating uncomplicated gonorrhea and urinary tract infections (UTIs). It is considered safe to use in pregnancy (pregnancy category B).¹⁶

Uncomplicated Gonorrhea

For treatment of uncomplicated gonorrhea, the Centers for Disease Control and Prevention (CDC) recommends ceftriaxone 125 mg IM once plus a 7

day course of doxycycline for the presumptive concurrent infection with *Chlamydia*. This regimen has a greater than 95% cure rate for anal and genital infections while also achieving cure rates of $\geq 90\%$ for pharyngeal infections. Another advantage for ceftriaxone is it may also abort incubating syphilis, a concern when treatment is not accompanied by a 7 day course of doxycycline. Cefuroxime axetil 1 g orally as a single dose is considered an alternative regimen. However, a single dose of this shorter-acting cephalosporin will not cover incubating syphilis nor *C. trachomatis*.¹⁷ Clinical trials conducted using 1–1.5 g single doses of cefuroxime axetil either alone or in combination with probenecid have produced cure rates of 96–100% in gonococcal genitoretal infections in both men and women.^{18–24} However, these high cure rates were not achieved in patients with pharyngeal gonococcal infections.²⁰ In comparative trials vs. amoxicillin plus probenecid, cefuroxime axetil was shown to be equally effective.^{19–21} There have been no comparative trials between cefuroxime axetil and ceftriaxone.

UTIs

The most commonly identified UTI pathogens include *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Cefuroxime axetil has been shown to be effective against these urinary pathogens, but provides broader coverage than necessary for most uncomplicated UTIs. The antibiotic of choice for the treatment of acute uncomplicated UTIs is trimethoprim in combination with sulfamethoxazole (TMP/SMX) or amoxicillin. For patients with an allergy to these agents, cefuroxime axetil is an expensive alternative. Several dosing regimens for treatment of UTIs have proved effective with cefuroxime axetil. In one clinical trial in non-pregnant women, single dose therapy with 1,000 mg resulted in a 88% clinical and bacteriological cure at 1 week post-therapy.²⁵ A slightly longer 3 day therapy trial with 125 mg twice daily had a similar efficacy, an 84.8% clinical cure.²⁶ The more traditional 7 day therapy 125 mg twice daily resulted in a 97% bacteriological cure at 1 week post-therapy.²⁷

COST

Table 2 represents the average wholesale price to the pharmacist for a 7 day supply of selected anti-

TABLE 2. Comparison of cost of commonly prescribed antibiotics used to treat obstetric and gynecological infections

Drug	Daily dosage ^a	AWP cost for 7 day supply ^b
Amoxicillin		
Generic	250 mg q 8 h	\$4.41
Amoxil®		\$4.54
Clavulanate potassium		
–Augmentin®	500 mg q 12 h	\$40.32
Cefaclor		
Generic	250 mg q 8 h	\$40.90
Ceclor®		\$46.49
Cefuroxime axetil–Ceftin®	250 mg q 12 h	\$44.94
	1 g \times 1 dose	\$12.84
Ceftriaxone–Rocephin®	125 mg IM \times 1	\$12.04
Doxycycline–generic	100 mg q 12 h	\$2.24
Trimethoprim-sulfamethoxazole		
Generic double-strength	1 tablet q 12 h	\$4.76
Bactrim DS®		\$17.50
Septra DS®		\$16.94

^aUsual adult dosage recommended by the manufacturer.

^bCost to the pharmacist based on average wholesale price (AWP) listings in Drug Topics Red Book (1996); cost to the patient may be higher.

biotics. These selected antibiotics represent either first-line choices for therapeutic indications such as gonorrhea, UTI, and skin/soft tissue infection, or in the case of cefaclor, have a similar spectrum of activity. In most cases, cefuroxime axetil is the more expensive choice with no increase in efficacy or safety.

CONCLUSIONS

Cefuroxime axetil is a broad spectrum β -lactam antibiotic. It has many approved indications, however, it is considered a second-line alternative. It is not the drug of choice for any infection, particularly those encountered in the field of obstetrics and gynecology. It is safe to use in pregnancy and has a low adverse effect profile, but due to its excessive acquisition cost and better therapeutic alternatives, it should be reserved for select cases.

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