Ceftizoxime: a third-generation cephalosporin active against anaerobic bacteria

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Ceftizoxime is a newly licensed parenteral antibiotic in the expanding family of third-generation cephalosporins. This broad-spectrum compound has a synmethoxyimino chain at the 7-position that confers β-lactamase stability.1 Ceftizoxime is active against aerobic gram-positive bacteria, including staphylococci, aerobic gram-negative bacilli and anaerobic bacteria. Its other properties include poor induction of β-lactamase2 and a long serum half-life.3

Mechanism of action and resistance

As with other β-lactam antibiotics ceftizoxime disrupts the cell-wall synthesis of susceptible organisms. In vitro, ceftizoxime shows a strong affinity for penicillin-binding proteins 1a, 1b and 3 of Escherichia coli4 and thus inhibits peptidoglycan cross-linkage for cell-wall synthesis, elongation and septation.

Resistance of gram-positive species such as Enterococcus faecalis to ceftizoxime is attributable to ineffective binding of the compound to the penicillin-binding proteins.5 Although the resistance of Listeria and certain species of Corynebacterium and Clostridium is not well understood it probably has the same basis.5 Enterobacteriaceae are sensitive to the drug except for certain strains of Enterobacter that produce β-lactamase, which can hydrolyze the compound. Resistance of Pseudomonas aeruginosa and Xanthomonas maltophilia arises from the inability of the drug to cross the outer cell membrane and reach the penicillin-binding proteins. Other Pseudomonas species, such as P. cepacia, and some Bacteroides fragilis strains are resistant because they hydrolyze the antibiotic.

In-vitro activity

Ceftizoxime’s spectrum of activity is similar to that of two other third-generation cephalosporins, cefotaxime and ceftriaxone. Like them, ceftizoxime is less potent against susceptible staphylococci than first-generation cephalosporins (e.g., cephalothin) but has an expanded spectrum of activity against aerobic gram-negative bacteria, as compared with first-generation and second-generation cephalosporins (cefuroxime and cefoxitin). As with cefotaxime and ceftriaxone, ceftizoxime does not have the antipseudomonal activity exhibited by cefoperazone and ceftazidime.

Ceftizoxime is active against the following gram-positive aerobic organisms: methicillin-susceptible staphylococci and streptococci, excluding enterococcal species.6,7 It is generally active against Enterobacteriaceae, including Citrobacter, Enterobacter, Serratia marcescens, Providencia stuartii and Morganella morgani. Most strains of Haemophilus influenzae,
including ampicillin-resistant strains, and Neisseria gonorrhoeae, including penicillinase-producing strains, are highly susceptible to ceftizoxime. Although some strains of P. aeruginosa are inhibited in vitro, most are considered resistant.

Controversy exists over ceftizoxime’s activity against anaerobic bacteria. Bacteroides is more susceptible to ceftizoxime than to cefotaxime or ceftriaxone. Some authors have reported that ceftizoxime is more active than cefoxitin against Bacteroides; however, others have disagreed. This discrepancy may be due to the different methods used for in-vitro susceptibility testing or the significant inoculum effect observed with ceftizoxime. Moreover, in an in-vivo study involving mice with combined E. coli and B. fragilis abscesses ceftizoxime was less effective than cefoxitin, cefotetan, ampicillin–sulbactam and imipenem–cilastatin against B. fragilis. Against other anaerobic bacteria ceftizoxime’s in-vitro activity is similar to that of cefoxitin.

Pharmacokinetic features

Because ceftizoxime is not absorbed from the gastrointestinal tract it is available only in parenteral form. After intravenous administration over 30 minutes of a single 1 g dose to healthy adults the serum concentration is 84.4 mg/L on average; the concentrations at 1, 2, 4 and 7 hours after the start of the infusion are 41.2, 16.4, 6.4 and 2.1 mg/L respectively. All of these serum levels are above the minimum inhibitory concentrations required for most gram-negative organisms except some strains of S. marcescens and Proteus.

After a dose of 1 to 2 g the drug distributes widely into body fluids and tissues, including pleural, ascitic and amniotic fluid, bile and sputum, prostate, uterus, gallbladder, heart and bone and cerebrospinal fluid with inflamed meninges. Tissue concentrations range from 14% to 46% of the serum concentrations. During meningitis therapy the mean cerebrospinal fluid level has been 8.53 mg/L, which is similar to that observed with cefotaxime and ceftriaxone. Only 31% of ceftizoxime is protein bound.

In adults with normal renal function the serum half-life of ceftizoxime is about 1.4 hours. Since the drug is not metabolized and is excreted principally in the urine, renal impairment results in higher serum levels and a prolonged serum half-life. Hemodialysis may reduce the serum levels by 50%.

Clinical trials

Ceftizoxime has been effective against susceptible organisms in open and controlled trials of genito-urinary and lower respiratory tract, skin, soft-tissue and intra-abdominal infections, bacteremia, gonorrhea, osteomyelitis and meningitis. Comparative agents for the treatment of genitourinary and lower respiratory tract, skin, soft-tissue and intra-abdominal infections have included cefamandole, cefoxitin, cefotaxime, tobramycin alone and the combination of clindamycin and tobramycin.

In these trials ceftizoxime was as effective as the comparative agents, although the study populations were generally too small to demonstrate a difference between the experimental and control groups. Cef-tizoxime treatment of bacterial meningitis due to susceptible organisms was effective in a limited number of adults and children. Also, ceftizoxime has been used successfully to treat febrile episodes in non-neutropenic cancer patients and infections in children.

For perioperative prophylaxis ceftizoxime has been found to be as effective as cefoxitin in cases of vaginal hysterectomy and elective colorectal surgery.

Adverse effects

The most common adverse effects are pain at the injection site (6.1%), thrombocytosis (4.5%), elevation in hepatic enzyme levels (3.0%), eosinophilia (2.9%), rash (0.8%), fever (0.7%), diarrhea (0.6%), nausea and vomiting (0.5%) and pruritus (0.4%). Partial cross-allergenicity among cephalosporins and penicillin can occur.

The prolonged use of ceftizoxime may result in the overgrowth of resistant organisms. Pseudomembranous colitis has been reported in 0.2% of patients.

Dosage

Ceftizoxime may be administered intramuscularly or intravenously. Uncomplicated urinary tract infections in adults generally respond to 500 mg every 12 hours. Moderately severe infections at other sites caused by susceptible bacteria should be treated with 1 g every 8 to 12 hours. Severe or complicated infections may require 1 g every 8 hours or 2 g every 8 to 12 hours. Life-threatening infections should be treated with 3 to 4 g every 8 hours intravenously. The maximum daily dose should not exceed 12 g. In children 50 mg/kg every 8 hours, up to 12 g/d, may be given for such infections as bacteremia, cellulitis and urinary tract infection.

If ceftizoxime is substituted for cefoxitin as prophylaxis in surgical procedures (amputation of a lower limb, appendectomy or colorectal surgery) 1 g should be administered intravenously just before surgery and be followed postoperatively by 1 g every 8 hours (two doses). When surgery is being per-
formed for perforated intestine or appendix due to penetrating abdominal trauma, therapy should generally last for 3 to 5 days, depending on the patient's clinical condition.

Adults should receive 500 mg intramuscularly for uncomplicated gonorrhea caused by penicillinase-producing or non-penicillinase-producing strains of *N. gonorrhoeae*. Meningitis due to susceptible gram-negative bacilli may be treated intravenously with 200 mg/kg daily divided into six equal doses; the total daily dose should not exceed 12 g.

Patients who have impaired renal function and a creatinine clearance of 50 to 79, 5 to 49 or less than 5 ml/min should receive 750 mg to 1.5 g every 8 hours, 500 mg to 1 g every 12 hours or 500 mg every 24 hours respectively. Those who undergo hemodialysis should be treated with 500 mg every 24 hours. However, if given in proximity to hemodialysis the dose should be administered after the procedure.

**Recommendations**

Because of the many third-generation cephalosporins available ceftizoxime's place in the hospital formulary is unclear. Its safety, spectrum of activity and clinical indications in both adults and children are the same as those of cefotaxime and ceftriaxone. Like them, ceftizoxime can be used (a) for serious community-acquired and nosocomial infections (pneumonia, bacteremia, osteomyelitis, and complicated urinary tract and skin infections) caused by susceptible aerobic gram-negative bacilli that are resistant to less expensive and narrower spectrum antibiotics, (b) for meningitis due to gram-negative organisms other than *P. aeruginosa*, (c) for uncomplicated gonococcal infections, (d) for infections due to susceptible aerobic gram-negative bacilli resistant to aminoglycosides and (e) as an aminoglycoside substitute for infections in patients with renal insufficiency. Ceftizoxime should not be used to treat pseudomonal infections.

The advantage of ceftizoxime over cefotaxime and ceftriaxone may be its increased activity against anaerobic bacteria, similar to that of cefoxitin. Ceftizoxime could therefore be used in mixed aerobic and anaerobic bone, skin, pelvic and intra-abdominal infections and for surgical prophylaxis. Although one might consider replacing cefotaxime, ceftriaxone and cefoxitin with ceftizoxime to reduce hospital costs and to streamline the formulary, such action is premature at present. As already mentioned, concerns still remain about ceftizoxime's inconsistent in-vitro activity against anaerobic bacteria, its stability against *Bacteroides β-lactamase* and its susceptibility to an inoculum effect. More data from randomized comparative clinical studies of ceftizoxime's effectiveness in mixed aerobic and anaerobic infections and gram-negative meningitis are required. Until such data are available ceftizoxime should not replace cefotaxime, ceftriaxone or cefoxitin in the hospital formulary.

**References**

3. American Hospital Formulary Service: Drug Information 89, American Society of Hospital Pharmacists, Bethesda, Md, 1989; 119-123
8. Chow AW, Finegold SM: In-vitro activity of ceftizoxime against anaerobic bacteria and comparison with other cephalosporins. Ibid: 45-50

*The costs of the 1-g and 2-g vials of the antibiotics are as follows: ceftriaxone $34 and $67, cefoxitin $16.94 and $33.33, cefotaxime $14.30 and $27.96 and ceftizoxime $11.25 and $22. The costs may vary from centre to centre.*


47. Guastella C: Cost savings realized from interchanging cefizoxime for cefoxitin. Am J Hosp Pharm 1988; 45: 2376-2377