

PRODUCT MONOGRAPH

**CEFOTAXIME for Injection USP
(cefotaxime sodium)**

Antibiotic

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PRODUCT MONOGRAPH

CEFOTAXIME for Injection USP (cefotaxime sodium)

500 mg, 1 g, and 2 g cefotaxime per vial

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

CEFOTAXIME for Injection USP (cefotaxime sodium) is a third generation semisynthetic cephalosporin antibiotic. Cefotaxime exerts its bactericidal action through the inhibition of bacterial cell wall synthesis. Cefotaxime is an aminothiazolyl cephalosporin and contains an aminothiazolyl-acetyl side chain, with an alpha-syn-methoximino group at position 7 of the cephalosporin nucleus. The aminothiazolyl side chain enhances antibacterial activity, particularly against Enterobacteriaceae, and the methoximino group imparts stability against hydrolysis by many β -lactamases.

INDICATIONS AND CLINICAL USE

Treatment

CEFOTAXIME for Injection USP (Cefotaxime sodium) may be indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

1. Lower respiratory tract infections such as pneumonia and lung abscess when caused by *Streptococcus pneumoniae*, other streptococci (excluding enterococci, e.g. *S. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Haemophilus influenzae* (including ampicillin resistant strains) and unspecified *Klebsiella* species.
2. Urinary tract infections caused by *Escherichia coli*, unspecified *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis*, indole positive *Proteus*, *Serratia marcescens* and *Staphylococcus epidermidis*. Also, uncomplicated gonorrhoea caused by *N. gonorrhoeae* including penicillin resistant strains.
3. Bacteremia/Septicemia caused by *Escherichia coli*, unspecified *Klebsiella* strains and *Serratia marcescens*.

4. Skin infections caused by *Staphylococcus aureus* (penicillinase and nonpenicillinase producing), *S. epidermidis*, Group A streptococci, *Escherichia coli*, *Proteus mirabilis* and indole positive *Proteus*.
5. Intra-abdominal infections caused by *Escherichia coli* and unspecified *Klebsiella* species.
6. Gynecological infections including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *E. coli*, Group A streptococci and *Staphylococcus epidermidis*; anaerobic bacteria including unspecified *Peptococcus* and *Peptostreptococcus* strains and some strains of *Bacteroides fragilis*.
7. Central nervous system infections such as meningitis and ventriculitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Escherichia coli*. Cefotaxime for Injection USP is not active against *Listeria monocytogenes*.

Prior to initiating therapy, specimens for bacteriologic culture should be obtained in order to isolate and identify the causative organisms and to determine their susceptibilities to cefotaxime. Therapy may be initiated while awaiting test results; however, antibiotic treatment may require re-evaluation once the results become available.

Clinical experience with CEFOTAXIME for Injection USP (cefotaxime sodium) in anaerobic infections is limited. Cefotaxime has been used with some success in intra-abdominal and wound infections against some strains of unidentified *Bacteroides* and anaerobic cocci.

CEFOTAXIME for Injection USP (cefotaxime sodium) has been shown to display activity against some strains of *Pseudomonas*.

CEFOTAXIME for Injection USP (cefotaxime sodium) has not shown impressive results in the treatment of infections in granulocytopenic and immunosuppressed patients.

CEFOTAXIME for Injection USP (cefotaxime sodium) should not be considered in the treatment of infections caused by enterococci, i.e. *Streptococcus faecalis*.

Prophylactic Use

CEFOTAXIME for Injection USP (cefotaxime sodium) may reduce the incidence of certain infections when administered perioperatively (pre-operatively, intra-operatively and post-operatively) as prophylactic treatment in patients undergoing elective surgical procedures (e.g. abdominal or vaginal hysterectomy, gastrointestinal and genito-urinary tract surgery), where contamination or potential contamination may occur.

Intra-operative (after clamping the umbilical cord) and post-operative cefotaxime administration in patients undergoing cesarean section may reduce the incidence of certain post-operative infections in patients who are at increased risk at developing such infections.

Effective use for elective surgery depends on the time of administration (see **DOSAGE AND ADMINISTRATION**).

Pre-operative bowel preparations by mechanical cleansing as well as with a nonabsorbable antibiotic (e.g. neomycin) is recommended for patients undergoing gastrointestinal surgery.

Should signs of infection arise, specimens for culture should be obtained, so that causative organisms can be identified and appropriate therapy may be instituted.

CONTRAINDICATIONS

CEFOTAXIME for Injection USP (cefotaxime sodium) is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium, the cephalosporins or the group of penicillin antibiotics.

WARNINGS

Hypersensitivity

BEFORE INITIATING THERAPY, CAREFUL ANALYSES SHOULD BE PERFORMED TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTAXIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. CEFOTAXIME FOR INJECTION USP SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS WHO HAVE EXPERIENCED TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. USE CAUTION WHEN ADMINISTERING ANTIBIOTICS, INCLUDING CEFOTAXIME FOR INJECTION USP TO PATIENTS WHO HAVE DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOTAXIME OCCURS, THE ANTIBIOTIC SHOULD BE DISCONTINUED AND APPROPRIATE TREATMENT SHOULD BE INSTITUTED (E.G. TREATMENT WITH EPINEPHRINE, ANTIHISTAMINES, PRESSOR AMINES OR CORTICOSTEROIDS).

***Clostridium difficile*-associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including CEFOTAXIME for Injection USP (cefotaxime sodium). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hemolytic Anemia

CEFOTAXIME FOR INJECTION USP SHOULD NOT BE USED IN PATIENTS WITH A HISTORY OF CEPHALOSPORIN-ASSOCIATED HEMOLYTIC ANEMIA SINCE THE RECURRENCE OF HEMOLYSIS IS MUCH MORE SEVERE.

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials, including CEFOTAXIME for Injection USP (cefotaxime sodium). Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2-3 weeks subsequent to the administration of CEFOTAXIME for Injection USP (cefotaxime sodium), the diagnosis of a cephalosporin-associated anemia should be considered and the drug discontinued until the etiology is determined.

Patients may benefit from periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing, where appropriate (see **ADVERSE REACTIONS**).

PRECAUTIONS

Patients with Gastrointestinal Disease

Caution should be exercised when prescribing CEFOTAXIME for Injection USP (cefotaxime sodium) to individuals with a history of lower gastrointestinal disease, particularly colitis.

Use in Obstetrics

The safety of CEFOTAXIME for Injection USP (cefotaxime sodium) in pregnancy has not yet been established. Benefits should be weighed against the possible risks to the mother and fetus when cefotaxime therapy is required in pregnant women. Consequently, before initiating cefotaxime therapy in women of child-bearing potential, the anticipated benefits must be weighed against the possible risks.

Nursing Mothers

CEFOTAXIME for Injection USP (cefotaxime sodium) is excreted in human breast milk in low concentrations. Caution should therefore be exercised when administering cefotaxime to nursing mothers.

Patients with Kidney Disease

Alterations in kidney function are rarely produced by CEFOTAXIME for Injection USP (cefotaxime sodium) therapy, however, evaluation of renal status is recommended, especially in severely ill patients receiving high doses.

A special dosage regimen is recommended in patients with markedly impaired renal function because normal dosage in these individuals is likely to produce excessive and prolonged serum concentration of the metabolites and prolonged serum antibiotic concentrations.

General

Prolonged use of cefotaxime may result in overgrowth of nonsusceptible organisms. It is essential to constantly evaluate the patient's condition. In the presence of superinfection, therapy should be discontinued and appropriate measures should be instituted.

Treatment with cephalosporins, including cefotaxime is known to give positive results in a direct Coomb's test.

In laboratory tests, a false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should be monitored.

ADVERSE REACTIONS

CEFOTAXIME for Injection USP (cefotaxime sodium) is generally well tolerated. Adverse reactions have usually been mild and transient and rarely required discontinuation of treatment. The most frequent adverse reactions with their frequency of occurrence are:

Hypersensitivity (1.8%)

Rash, pruritis and fever have been noted (see **WARNINGS**).

Local (5%)

Inflammation at the site of injection has occurred with intravenous administration. Some degree of pain and tenderness have been experienced after intramuscular injection. Induration has occasionally been reported.

Gastrointestinal (1.7%)

Colitis, diarrhea, nausea and vomiting have been reported rarely. Symptoms of pseudomembranous colitis have appeared during and after cefotaxime treatment (see **WARNINGS**).

Hematological (<1%)

Mild reversible leukopenia, neutropenia, eosinophilia, thrombocytopenia and agranulocytosis have been reported. Some individuals may develop positive direct Coomb's tests during therapy with cefotaxime. Cases of hemolytic anemia have been reported (see **WARNINGS**).

Genitourinary system (<1 %)

Moniliasis and vaginitis have occasionally been reported.

Liver (<1 %)

Transient elevations in SGOT, SGPT, serum LDH and serum alkaline phosphatase levels have been reported.

Kidney (<1 %)

Elevations in serum creatinine and/or blood urea nitrogen levels have been observed.

Central Nervous System (0.2%)

Headache.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Since no case of overdose has been reported to date with CEFOTAXIME for Injection USP (cefotaxime sodium), no specific information on symptoms or treatment is available. Treatment of overdose should be symptomatic.

DOSAGE AND ADMINISTRATION

CEFOTAXIME for Injection USP (cefotaxime sodium) may be administered intravenously or intramuscularly after reconstitution (see Table with recommended mode of reconstitution according to route of administration).

Dosage**Adults**

Dosage and route of administration depend on severity of infection, susceptibility of the causative organisms, and the patient's condition. The usual adult dosages are shown in the table below.

Guidelines for Dosage of Cefotaxime for Injection USP (cefotaxime sodium)

Type of infection	Daily Dose (g)	Frequency and Route
Uncomplicated Gonorrhoea	1	1 g i.m. (single dose)
Uncomplicated infections	2	1 g every 12 hours i.m. or i.v.
Moderately severe to severe infections	3 – 6	1-2 g every 8 hours i.m. or i.v.
Very severe infections (e.g. septicemia, CNS)	6 – 8	2 g every 6-8 hours i.v.
Life-threatening infections	up to 12	2 g every 4 hours i.v.

To prevent postoperative infection in contaminated or potentially contaminated surgery, the following doses are recommended:

- (a) 1 g i.m. or i.v. administered 30 minutes to 90 minutes prior to initial surgical incision to ensure that adequate antibiotic levels are present in the serum and tissues at the start of surgery.
- (b) 1 g i.m. or i.v. administered 90 minutes to 2 hours following the first dose; for lengthy operative procedures, additional intraoperative doses may be administered, if necessary, at appropriate intervals (90 minutes to 2 hours) during surgery.
- (c) 1 g i.m. or i.v. administered within 2 hours following completion of surgery.

The total cumulative prophylactic dose should not exceed 6 g in a 12 hour period.

Cesarean Section:

The first 1 g dose should be administered intravenously as soon as the umbilical cord is clamped. The second and third 1 g doses should be given intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants and Children:

The following dosage schedule is recommended:

Neonates:

0 - 1 week of age 50 mg/kg every 12 hours i.v.

1 - 4 weeks of age 50 mg/kg every 8 hours i.v.

Infants and children (1 month to 12 years of age): For body weights less than 50 kg*, the recommended daily dose is 50 to 100 mg/kg i.m. or i.v. divided into 4 to 6 equal doses, or up to 180 mg/kg/day for severe infections (including central nervous system infections).

*For body weights 50 kg or more, the usual adult dosage should be used.

THE MAXIMUM DAILY DOSE SHOULD NOT EXCEED 12 GRAMS

Cefotaxime therapy should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained. A minimum of 10 days of treatment is recommended for infections caused by Group A beta-haemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis.

During therapy of chronic urinary tract infection, frequent clinical and bacteriologic evaluation is necessary and may be required for several months after completion of treatment. Persistent infections may require several weeks of treatment. Doses less than those recommended above should not be employed.

Dosage for Patients with Impaired Renal Function:

In patients with estimated creatinine clearance of less than 20 mL/minute/1.73m², the dose of cefotaxime should be halved.

If only serum creatinine values are available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance.

Males: $\text{Weight (kg)} \times (140 - \text{age})$
 $72 \times \text{serum creatinine}$

Females: 0.85 x above value

ADMINISTRATION**Intramuscular**

Intramuscularly administered CEFOTAXIME for Injection USP (cefotaxime sodium) should be injected into a large muscle mass such as the upper quadrant of the buttock (i.e. gluteus maximus). Maintain aspiration to avoid inadvertent injection into a blood vessel.

Intravenous

The intravenous route is preferable for patients with bacteremia, bacterial septicemia or other severe life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For bolus administration, a solution containing 1 or 2 g of cefotaxime can be injected over a period of 3 to 5 minutes. Using an infusion system, it may also be given over a longer period of time through the tubing by which the patient is receiving other parenteral solutions. Butterfly or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing cefotaxime sodium, it is advisable to temporarily discontinue administration of any other infusion solution at the same site.

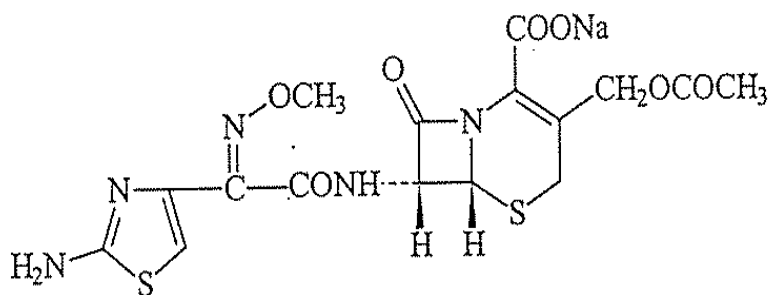
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: cefotaxime sodium

Chemical name: 5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 3-[(acetyloxy) methyl] -7- [[(2-amino-4-thiazolyl) (methoxyimino) -acetyl] amino] -8- oxo, monosodium salt, [6R-[6 α , 7 β (Z)]]-

Structural formula:



Molecular formula: C₁₆H₁₆N₅NaO₇S₂

Molecular weight: 477.5

Description: Cefotaxime sodium is a white to pale yellow crystalline powder. It is soluble in water at about 20%, but poorly soluble in common organic solvents including ethanol. A 10% solution of cefotaxime sodium has a pH of between 4.5 and 6.5 and a pka of 3.4.

Composition

Each vial contains cefotaxime sodium equivalent to 500 mg, 1 g, or 2 g of cefotaxime base.

Stability and Storage Recommendations: The dry powder should be stored between 15° and 25 °C protected from light. The dry powder tends to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

RECONSTITUTION

For intramuscular use, reconstitute CEFOTAXIME for Injection USP (cefotaxime sodium) with either Sterile Water for Injection or Bacteriostatic Water for Injection according to the following reconstitution table:

Reconstitution Table - Intramuscular Use

Strength	Volume of Solvent*	Approx. Avail. Volume	Approx. Average Concentration
500 mg vial	2 mL	2.2 mL	230 mg/mL
1 g vial	3 mL	3.4 mL	300 mg/mL
2 g vial	5 mL	6.0 mL	330 mg/mL

* Shake to dissolve

For direct intravenous injection (bolus) and/or continuous intravenous infusion the 500 mg, 1 g, and 2 g vials of Cefotaxime for Injection USP should be reconstituted with at least 10 mL of Sterile Water for Injection to the concentrations listed in the table below:

Reconstitution Table - Intravenous Use

Strength	Volume of Solvent*	Approx. Avail. Volume	Approx. Average Concentration
500 mg vial	10 mL	10.2 mL	50 mg/mL
1 g vial	10 mL	10.4 mL	95 mg/mL
2 g vial	10 mL	11.0 mL	180 mg/mL

*Shake to dissolve

CEFOTAXIME for Injection USP (cefotaxime sodium) reconstituted in its original vial maintains satisfactory potency for 24 hours at room temperature (25°C) and for 48 hours under refrigeration.

Solutions of cefotaxime sodium range from light yellow to amber, depending on the concentration and the solvent used. The solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

Parenteral Products:

The reconstituted solution may be further diluted with 50 to 1000 mL of the following fluids recommended for intravenous infusion:

Diluents for I.V. infusion:

- Sodium Chloride Injection, 0.9%
- Dextrose Injection, 5%
- Sodium Chloride, 0.9% and Dextrose Injection, 5%
- Sodium Chloride, 0.45% and Dextrose Injection, 5%
- Sodium Chloride, 0.2% and Dextrose Injection, 5%
- Dextrose, 5% and Potassium Chloride Injection, 0.15%
- Ringer's Injection
- Lactated Ringer's Solution
- Lactated Ringer's with Dextrose injection, 5%

A solution of 1 g of cefotaxime sodium in 14 mL of sterile water for injection is isotonic.

Only freshly constituted solutions may be further diluted with 50 to 1000 ml of the recommended infusion fluids. Such solutions should be used within 18 hours when stored under refrigeration or within 4 hours when stored at room temperature. Any unused portion should be discarded.

Solutions of cefotaxime sodium exhibit maximum stability in the pH 5 to 7 range.

Special instructions

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. The dry powder as well as the solutions tend to darken, depending on storage conditions.

Incompatibilities

Solutions of cefotaxime sodium like those of most β -lactam antibiotics, should not be added to aminoglycoside solutions (for example, gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction. If cefotaxime sodium solutions and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection. Solutions of cefotaxime sodium should not be prepared with diluents having a pH above 7.5 such as Sodium Bicarbonate Injection.

AVAILABILITY OF DOSAGE FORMS

CEFOTAXIME for Injection USP (cefotaxime sodium) is supplied as a sterile white to yellow powder in vials containing 500 mg, 1 g, or 2 g of cefotaxime base.

MICROBIOLOGY

CEFOTAXIME for Injection USP (cefotaxime sodium) has in vitro activity against a wide range of gram-positive and gram-negative organisms as observed in the following tables.

SENSITIVITY OF AEROBIC AND ANAEROBIC BACTERIA TO CEFOTAXIME

MICROORGANISMS	CUMULATIVE PERCENTAGE OF STRAINS INHIBITED AT INDICATED CONCENTRATIONS* (g/mL)										
	No. of Strains	≤0.1	0.5	1.0	2.0	4.0	8.0	16	32	64≥	128
AEROBES											
GRAM-NEGATIVE											
<i>Achromobacter xylosoxidans</i>	4									50	90
<i>Acinetobacter</i> sp.	39	5	10	18	28	38	62	72	87	90	100
<i>Acinetobacter anitratum</i>	154				6	13	43	71	83	87	100
<i>Acinetobacter Iwoffii</i>	15			50	90		100				
<i>Aeromonas hydrophila</i>	8	90		100							
<i>Citrobacter</i> sp	47	60	74	74	77	79	85	89	94	98	100
<i>Citrobacter diversus</i>	25	100									
<i>Citrobacter freundii</i>	28	79	93	96				100		28	79
<i>Commamonas terrigena</i>	5				50	90					
<i>Edwardsiella tarda</i>	2	100									
Enterobacteriaceae sp.	6083		91	95	99	100					
<i>Enterobacter</i> sp	61	79	90	95	98						
<i>Enterobacter aerogenes</i>	57	88	89	91		95		98		100	
<i>Enterobacter cloacae</i>	80	63	69	74	84	88				94	100
<i>Escherichia coli</i> ^a	657	95	98	99						100	
<i>Haemophilus</i> Sp. ^a	294	97	99	100							
<i>Haemophilus influenzae</i> ^a	113	96	98	99						100	
<i>Haemophilus parainfluenzae</i>	1	100									
<i>Klebsiella</i> sp.	101	91	97	100							
<i>Klebsiella oxytoca</i>	10			20	50	60	70	80	90	100	
<i>Klebsiella pneumoniae</i> ^a	226	88	98	99	100						
<i>Levinea</i>	6	67				83		100			
<i>Moraxella</i> sp.	6	50	67			83	100				
<i>Neissera</i> sp.	12	75	100								

MICROORGANISMS	CUMULATIVE PERCENTAGE OF STRAINS INHIBITED AT INDICATED CONCENTRATIONS* (g/mL)										
	No. of Strains	≤0.1	0.5	1.0	2.0	4.0	8.0	16	32	64≥	128
Neissera catarrhalis	2	100									
Neisseria gonorrhoeaea	472	100									
Neisseria meningitidis	150				50	90					
Pasteurella sp.	5	90									
Proteus indole (+)	102	64	75	85	94	96		97		100	
Proteus indole (-)	20	90				95				100	
Proteus mirabilis (-)	186	98		100							
Proteus morganii (+)	9	100									
Proteus rettgeri (+)	7	50		90							
Providencia sp.	37	35	54	78	86	95		100			
Pseudomonas sp.	136		1		3	9	28	57	72	85	100
Pseudomonas aeruginosa	1412				1	6	30	69	85	97	100
Pseudomonas maltophilia	12								50	90	100
Pseudomonas putida	10							50		90	100
Pseudomonas putrefaciens	4	50			90						
Salmonella sp.	33	79	97		100						
Salmonella typhi	30	100									
Serratia sp.	93	29	43	47	52	54	58	63	78	95	100
Serratia marcescens ^a	86	35	41	44	50	65	81	97	100		
Shigella sp.	19	74	84	95	100						
Vibrio sp.	4	90									
Yersinia enterocolitica	1	100									
GRAM – POSITIVE											
Staphylococcus aureus	1686		5	16	89	95	100				
Staphylococcus epidermidis	175	20	45	57	73	89	99			100	
Streptococcus A	12	100									
Streptococcus B	20	90	100								

MICROORGANISMS	CUMULATIVE PERCENTAGE OF STRAINS INHIBITED AT INDICATED CONCENTRATIONS* (g/mL)										
	No. of Strains	≤0.1	0.5	1.0	2.0	4.0	8.0	16	32	64≥	128
Streptococcus enterococcus	146		1	5	10	14	17	20	21	25	100
Streptococcus D non-enterococcus	23	70	87	98	100						
Streptococcus pneumoniae	67	91									
ANAEROBES											
GRAM- NEGATIVE											
Actinomyces israelii	1	100									
Barteroides sp.	51		4		20	26	38	60	82	94	100
Bacteroides fragilis	28						50	90			
Bacteroides fragilis 900/76	1		100								
Bacteroides fragilis 466/76	1				100						
Bacteroides thetaiota-micron	13							50		90	
Fusobacterium sp.	5	50	90								
Fusobacterium mecropharum 696D	1	100									
Veillonella sp.	1	50	100								
GRAM – POSITIVE											
Clostridium sp. (Other than C. diff.)	13	15			61	84	100				
Clostridium perfringes	19		50			90					
Cocci	11	50	90								
Propionibacterium	11	90									
Staph. anaerobius 5448	1	100									
Staph. charolyticus 6041	1		100								
Strept. anaerobius 580A	1		100								

* Serial dilutions (broth and agar methods)

^a Includes producers and non-producers of β-lactamases

Beta-lactamase Stability

The sensitivity to β -lactamases was determined by a cell-free *in vitro* test system using characteristic β -lactamases of various Richmond classes. Evidence was found of the stability of cefotaxime against the inactivating effect of cephalosporinases from *Enterobacter cloacae* P 99 (Class Ia) and *Pseudomonas* HS 18 (Id), as well as against that of the β -lactamases from *Escherichia coli* TEM (IIIa). Cefotaxime was only mildly sensitive to the effects of the enzyme formed by *Klebsiella aerogenes* 1082 E (IVc). The following table summarizes the effect of β -lactamase on cefotaxime.

EFFECT OF β -LACTAMASE ON CEFOTAXIME

Enzyme Source	CEFOTAXIME	
	Relative β -Lactamase Sensitivity	MIC (μ g)
<i>E. cloacae</i> P 99	0%	125
<i>P. aeruginosa</i> HS 18	0%	1.0
<i>E. coli</i> TEM	0%	0.078
<i>K. aerogenes</i> 1082 E	2.5%	12.5

Initial count for each organism about 5×10^4 C.F.U. per mL in each tube. There is *in vitro* evidence of synergy between cefotaxime and aminoglycoside antibiotics (gentamicin and tobramycin) against some strains of *Pseudomonas*.

A broth dilution checkerboard synergy assay was used to assess the activity of cefotaxime, cefoperazone, moxalactam, and carbenicillin, in combination with tobramycin, against 38 strains of *Pseudomonas aeruginosa*. Synergy occurred significantly more often ($P \leq 0.001$) when tobramycin was combined with cefotaxime (63%) than when it was combined with carbenicillin (26%), cefoperazone (21%), or moxalactam (18%). Of the 25 synergistically inhibited strains, the combination of cefotaxime and tobramycin was synergistic against 24 and was the only synergistic combination against 10. Of the six strains initially resistant to cefotaxime, five were susceptible to this agent (minimum inhibitory concentration, $\leq 32 \mu\text{g/mL}$) when it was combined with tobramycin.

The results of synergy testing against 38 strains of *Pseudomonas aeruginosa* are shown in the following table.

Results of Synergy Testing Against 38 Strains of *Pseudomonas aeruginosa*

Antibiotic Combination	Number (%) Synergistic
Tobramycin + Cefotaxime*	24 (63.2)
Tobramycin + Carbenicillin	10 (26.3)
Tobramycin + Cefoperazone	8 (21.1)
Tobramycin + Moxalactam	7 (18.4)

* $P \leq 0.001$ for Tobramycin + Cefotaxime versus each of the other combinations (McNemar test). Differences among the other antibiotic combinations were not statistically significant.

In another study, the combination of cefotaxime and gentamicin was tested against 111 clinical isolates of *Pseudomonas aeruginosa* and was found to have a synergistic effect against 74% of the strains tested.

Susceptibility Plate Tests

With the Bauer-Kirby-Sherris-Turck method of disc susceptibility, the zones of inhibition produced when a disc containing 30 µg of cefotaxime is used should be interpreted according to the following criteria:

Interpretation	Zone Diameter (mm)
Susceptible	≥ 20
Intermediate	15 – 19
Resistant	≤ 14

Since certain strains of Enterobacteriaceae have been shown to be resistant to the cephalosporin class disc, only the cefotaxime discs must be used for testing the susceptibility of cefotaxime.

PHARMACOLOGY

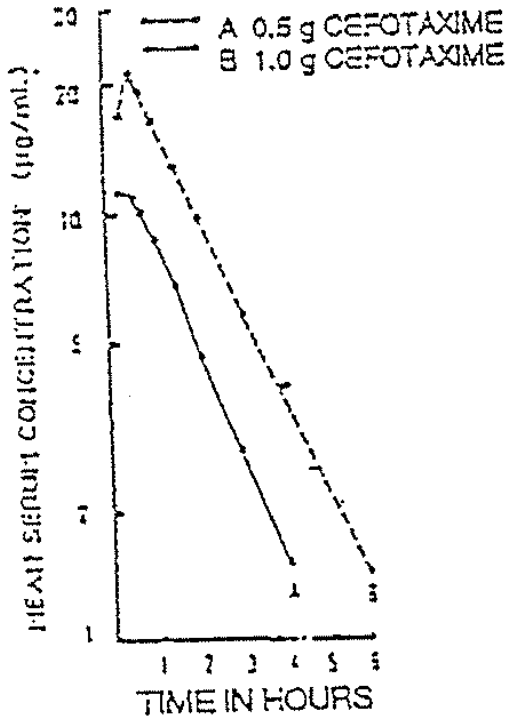
ANIMAL PHARMACOLOGY

Cefotaxime used in animal studies demonstrated no significant effect on the central nervous system, cardiovascular and respiratory systems, kidneys, blood clotting mechanisms and blood glucose levels.

HUMAN PHARMACOLOGY AND KINETICS

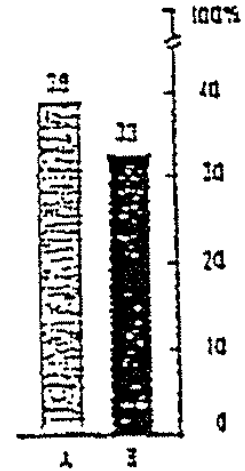
Following intramuscular administration of a single 500 mg or 1 g dose of cefotaxime to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 µg/mL respectively are attained within 30 minutes and decline with an elimination half-life of approximately 1 hour.

INTRAMUSCULAR ADMINISTRATION



Mean serum concentrations of cefotaxime administered intramuscularly as a single dose of 500 mg and 1 g.

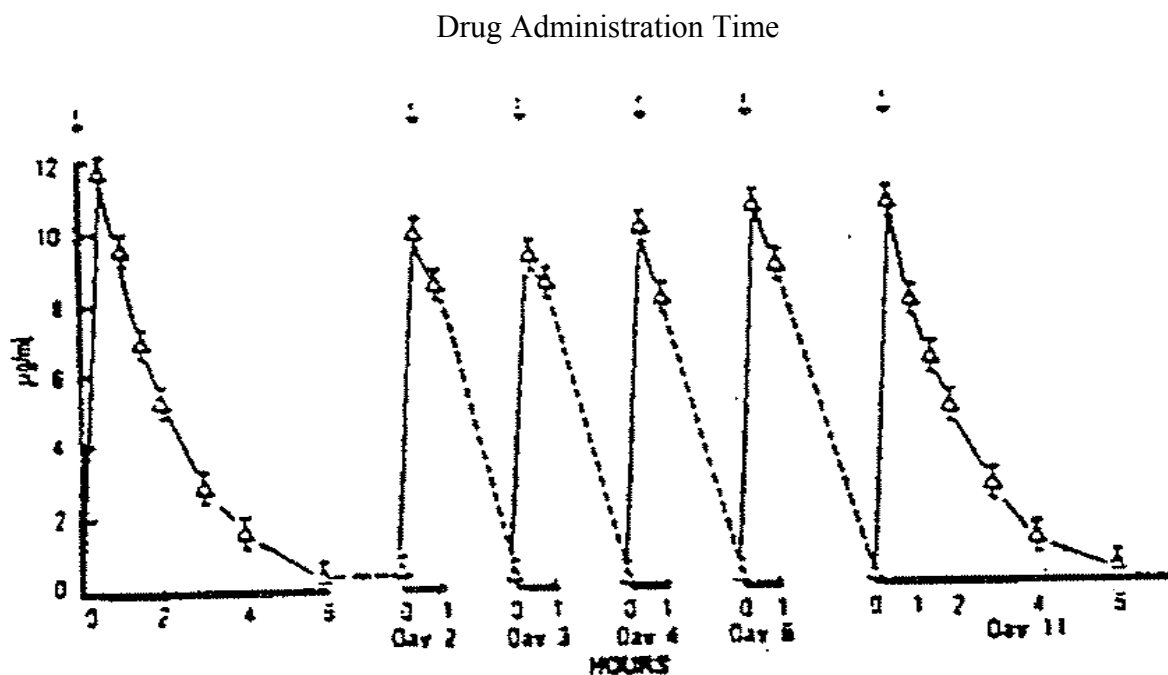
% of administered dose found in urine from 0 to 24 hours



Cumulative urinary recovery of cefotaxime after intramuscular injection of 500 mg and 1 g.

Kinetic Parameters	500 mg	1000 mg
Peak serum level ($\mu\text{g/mL}$)	11.7 ± 0.7	20.5 ± 1.8
Time to peak (hrs)	0.4 ± 0.04	0.5 ± 0.06
AUC ₍₀₋₈₎ ($\mu\text{g/mL/hrs}$)	23.2 ± 1.2	45.7 ± 3.1
$t_{1/2 \beta}$ (hrs)	1.2 ± 0.05	1.3 ± 0.1
Cl _s (mL/min/1.73m ²)	315.6 ± 19	318.5 ± 19.9
% unchanged drug in urine/ 0-24 hrs	38.8	33.3
Cl _r (mL/min/1.73m ²)	122.4 ± 20	103.8 ± 10.8

Following multiple intramuscular injections, serum levels at 30 minutes after a dose of 500 mg of cefotaxime every 8 hours, ranged from 9.2 to 11.9 $\mu\text{g/mL}$. There was no difference between the half-life (hr) at Day 1 and Day 11, but differences were noted in the AUC₀₋₈ hours fractional serum clearance and renal clearance; the latter probably being related to significantly lower recovery of the drug on Day 11.



Mean serum levels \pm SE of cefotaxime administered after multiple doses of 500 mg cefotaxime administered by intramuscular injection every 8 hours.

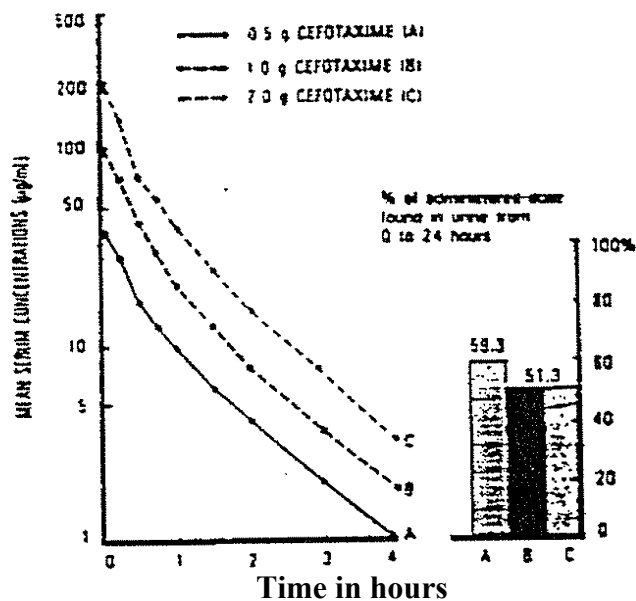
Kinetic Parameters of cefotaxime after multiple intramuscular injections of 500 mg (mean ± SE).

	Day 1	Day 11
Elimination rate constant (β) (hr^{-1})	0.778 ± 0.04	0.784 ± 0.04
$t_{1/2}$ (hr)	0.93 ± 0.05	0.92 ± 0.05
AUC ₍₀₋₈₎ ($\mu\text{g/mL/hr}$)	24.28 ± 1.18	19.91 ± 1.25
Fractional Serum Clearance ($\text{mL/min}/1.73 \text{ m}^2$)	304.8 ± 13.49	377.3 ± 23.61
Volume of Distribution ($\text{L}/1.73 \text{ m}^2$)	23.96 ± 1.07	29.68 ± 2.58
Renal clearance ($\text{mL/min}/1.73 \text{ m}^2$)	194.4 ± 18.35	146.6 ± 13.86
Drug Excreted 0 - 6 hr (%)	62.6 ± 5.09	39.1 ± 3.77

Intravenous Administration

There is a dose dependent increase in serum levels after the i.v. administration of 500 mg, 1 g and 2 g of cefotaxime (38.9, 101.7, and 214.4 $\mu\text{g/mL}$ respectively), without alteration in the elimination half-life.

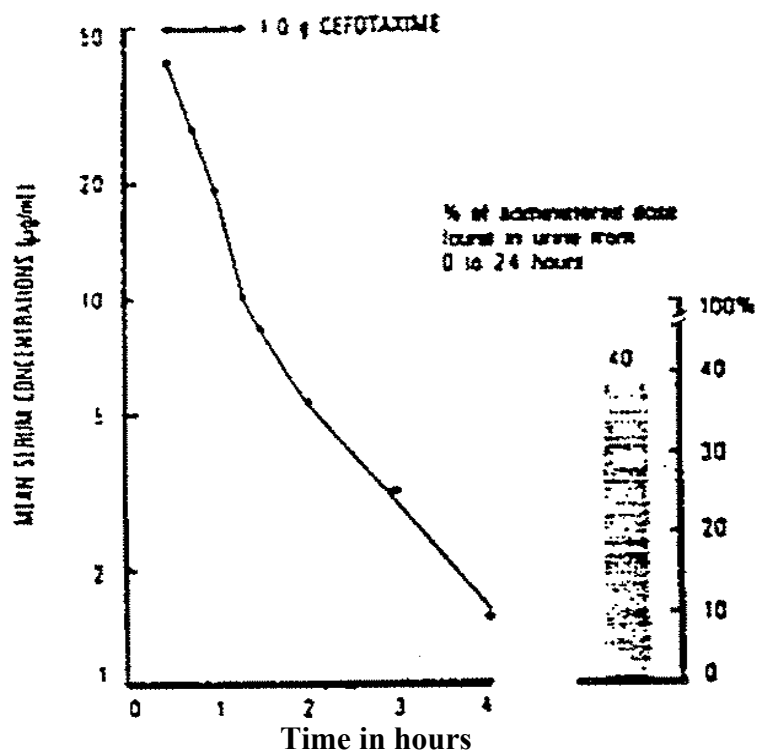
Intravenous Administration



Mean serum concentrations of cefotaxime administered intravenously as a single dose of 0.5 and 1.0 and 2.0 g to healthy male volunteers.

Kinetic Parameters	Cefotaxime		
	500 mg	1000 mg	2000 mg
Peak Serum level ($\mu\text{g/mL}$)	37.9 ± 2.1	102.4 ± 9.9	214.1 ± 18.7
AUC_{0-8} ($\mu\text{g/mL/hr}$)	30.6 ± 2.2	70.4 ± 3.9	134.1 ± 8.4
$t_{1/2\beta}$ (hrs)	1.04 ± 0.07	1.04 ± 0.06	0.86 ± 0.05
Cl_s ($\text{mL/min}/1.73\text{m}^2$)	245.3 ± 19.5	206.8 ± 13.1	215.1 ± 14.1
% unchanged drug in urine/ 0-24 hrs	59.3	51.3	51.3
Cl_r	146.8 ± 18.6	104.0 ± 9.7	110.4 ± 10.7

Administration of 1.0 g of cefotaxime intravenously over 30 minutes gave a mean peak serum concentration at the end of the 30 minutes of $41.1 \mu\text{g/mL}$ with an elimination half-life of 1.13 hours.



Mean Serum Concentrations of cefotaxime infused intravenously over 30 minutes as a single dose of 1 g.

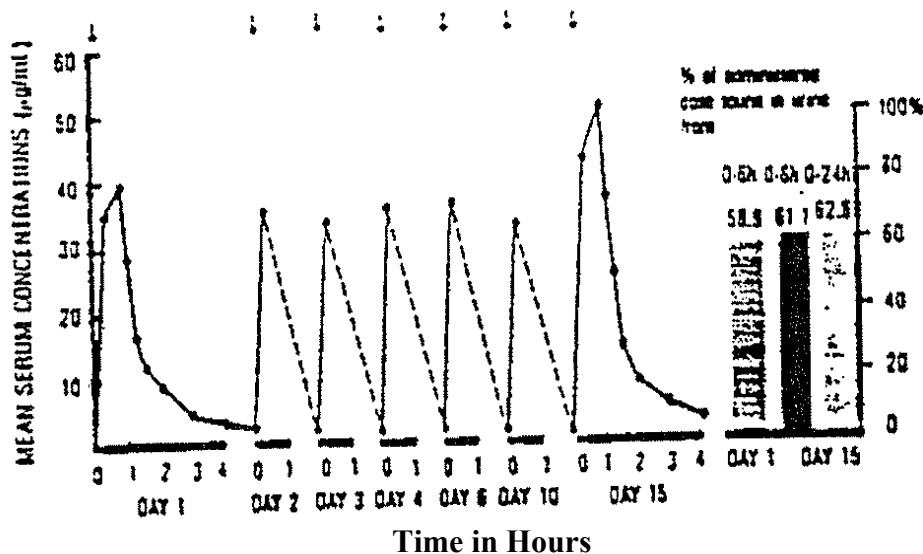
Cumulative urinary recovery of cefotaxime after intravenous infusion of 1 g.

Kinetic Parameters	Cefotaxime 1000 mg
Peak Serum level at end of 30 minutes ($\mu\text{g/mL}$)	41.1
AUC_{0-8} ($\mu\text{g/mL/hr}$)	44.3
$t_{1/2\beta}$ (hrs)	1.13
Cl_s ($\text{mL/min}/1.73\text{m}^2$)	341.6
% unchanged drug in urine/ 0-24 hrs	40.0
Cl_r ($\text{mL/min}/1.73\text{m}^2$)	130.1

There was no evidence of drug accumulation following repetitive intravenous infusion over 30 minutes of 1.0 g doses every 6 hours for 14 days.

The biological half-life was approximately 1.0 hour and the 24 hour urinary excretion of unchanged drug amounted to 62.6% of the administered dose (almost all of it in the first 6 hours).

Drug Administration Time



Mean serum concentration of cefotaxime infused intravenously over 30 minutes as a single dose of 1.0 g and every 6 hours for 14 days (D) to health male volunteers.

	Cefotaxime 1000 mg	
	Day 1	Day 15
AUC_{0-8} ($\mu\text{g/mL/hr}$)	56.9 ± 2.09	68.69 ± 3.49
$t_{1/2\beta}$ (hrs)	1.16 ± 0.07	1.03 ± 0.07
Cl_s ($\text{mL/min}/1.73\text{m}^2$)	259.3 ± 9.03	219.4 ± 9.50
% unchanged drug in urine/ 0-6 hrs	58.9	61.1
% unchanged drug in urine/ 0-24 hrs	--	62.6
Cl_r ($\text{mL/min}/1.73\text{m}^2$)	154.5 ± 11.91	132.9 ± 6.72

Cerebrospinal Fluid Penetration

Cefotaxime diffused consistently and in therapeutic levels into the cerebrospinal fluid of 13 children (aged 9 days to 5 years) with bacterial meningitis. Cerebrospinal fluid levels early (6.0 µg/mL) and late (1.2 µg/mL) in treatment were 17 to 275-fold the MBC's for the infecting organisms. Following a single 40 mg/kg intravenous dose to each of 5 infants (aged 1 to 19 months) with ventriculostomies, mean cerebrospinal fluid levels of cefotaxime were 6.4, 5.7, and 4.5 µg/mL at 2, 4, and 6 hours, respectively. Cefotaxime mean half-life in 4 infants was 1.15 ± 0.58 hours in plasma and 4.3 ± 3.1 hours in cerebrospinal fluid.

CEFOTAXIME AND DESACETYL CEFOTAXIME PLASMA AND CSF LEVELS AFTER I.V. INJECTION IN CHILDREN WITH BACTERIAL MENINGITIS

DRUG	Drug level (g/mL)*					
	Early (36 - 48 h)			Late (14 days)		
	Plasma	CSF	Diffusion ratio (%)	Plasma	CSF	Diffusion ratio (%)
Cefotaxime	5.1-55.7 (16.7±14.7)	0.74-38.8 (6.0±10.2)	7.0-69.7 (27.7±16.2)	1.7-13.6 (6.6±4.3)	0.6-3.1 (1.2±0.9)	4.5-64.7 (25.7±21)
Desacetyl cefotaxime	2.5-20.1 (8.1±4.2)	0.89-27.4 (4.6±7.0)	12.2-219 (51.9±54.5)	1.5-9.5 (5.4±1.9)	0.5-2.1 (1.1±0.8)	8.9-40.0 (20.8±9.3)

*Values in parentheses represent the mean ±standard deviation

Thirty -two (32) cases of adult meningitis received cefotaxime, 2 g every 8 hours by bolus injection (3 - 5 minutes). Mean concentration of cefotaxime in cerebrospinal fluid ranged from 0.8 µg/mL (aseptic meningitis), to 6.4 µg/mL (Gram-negative and *Listeria monocytogenes*), and from 0.5 to 5.4 µg/mL for the metabolite.

Pediatric Pharmacokinetics

A single 50 mg/kg dose of cefotaxime was intravenously infused over 10 minutes to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with birth weights less than or equal to 1500 g, regardless of age was found to be longer (4.6 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 g. Mean serum clearance was also lower in the smaller birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age (see **DOSAGE AND ADMINISTRATION**).

	Group I (≤ 1500 g at birth and < 5 days old)	Group II (> 1500 g at birth and < 5 days old)	Group III (varying birth weight and ≥ 5 days old)	Group A ≤ 1500 grams	Group B > 1500 grams
AUC _{0-6 hrs} (μg/ml.hr)	394	418	375	400	392
AUC _{0-∞ hrs} (μg/ml.hr)	683	620	551	675	561
Half-life (hrs)	4.9	3.7	3.5	4.6	3.4
V _d (L/kg)	0.53	0.44	0.45	0.51	0.44
Cl _s (mL/min/1.73m ²)	22.5	38.8	39.1	23.0	43.9

Renal Insufficiency

Cefotaxime in a dose of 1.0 g was injected intravenously twice daily for 4 to 7 days to 9 patients with renal insufficiency. These patients had creatinine clearances ranging from 5.0 to 25.5 mL/minute/1.73 m². The following table summarizes the pharmacokinetics of cefotaxime and its metabolites when 1.0 g of cefotaxime was administered daily to patients with renal failure.

PHARMACOKINETICS^a (mean values)

Parameter	Cefotaxime		DAC ^b		UP1 ^c		UP2 ^d	
	1 st Dose	Last Dose	1 st Dose	Last Dose	1 st Dose	Last Dose	1 st Dose	Last Dose
Peak Plasma Level (μg/mL)	--	--	19.3	37.3	5.0	17.2	4.5	14.7
C _{max} (last dose)	1.2		2.0		4.2		3.9	
C _{max} (first dose)	1.3		1.7		3.1		3.0	
Time to peak (hrs)	--	--	5.1	3.7	6.5	6.0	6.2	6.0
Distribution half-life (hrs)	0.5	0.7	--	--	--	--	--	--
Biological t _{1/2} (hrs)	2.9	3.1	10.4	11.5	6.2	16.6	8.1	21.1
AUC _{0-∞} (mcg/mL/hrs)	280	351	331	722	106	605	115	538
AUC _{0-12 hrs} (last dose)	1.3		1.7		3.1		3.0	
AUC _{0-12 hrs} (first dose)	1.3		1.7		3.1		3.0	
Renal Clearance (mL/minute)	13.0	--	14.8	--	30.2	--	30.9	--
Cumulative urinary excretion (mg)	171.4	137.7	127.8	154.4	84.5	142.0	75.3	133.7

a Data in the table above represent mean values; b DACM represents desacetyl cefotaxime, a metabolite of cefotaxime; c UP1 is a metabolite of cefotaxime; d UP2 is a metabolite of cefotaxime;

The half-lives of cefotaxime, desacetyl cefotaxime, UP1 and UP2 were longer and renal clearances were decreased in these patients with renal insufficiency. The biological half-life of cefotaxime was 2.9 hours after the first dose and 3.1 hours after the fifth dose. Neither the drug nor its metabolites accumulated even when clearances were as low as 20 mL/minute/1.73 m².

However, in patients with creatinine clearances approaching 5 mL/minute/1.73 m², accumulation of the metabolites becomes apparent.

Consequently, until further clinical experience is obtained in such patients, it is recommended that the dose of cefotaxime be halved when creatinine clearance is lower than 20 mL/minute/1.73 m².

Metabolism and Excretion

The metabolism of cefotaxime in humans is a two-step process. Cefotaxime is first partially metabolized by non-specific esterases to form desacetyl cefotaxime (DACM). Further metabolism follows with subsequent conversion to open β -lactam ring structure (UP1) and (UP2).

DACM has been shown to account for 10 to 15% of the bactericidal activity of the parent compound. It has no activity against *Pseudomonas*. UP1 and UP2 both lack antibacterial activity.

Approximately 20 to 36% of an intravenous dose of cefotaxime is excreted by the kidneys as unchanged drug, 15 to 25% as the DACM derivative, and 20 to 25% as UP1 and UP2 combined. Approximately 10% of the administered dose is recovered in the feces.

No disulfiram-like reaction has been reported to occur with the use of cefotaxime.

Protein Binding

In dialysis tests, about 51 % (range 35 - 64%) of cefotaxime was found to be bound to human serum proteins at concentrations from 6.25 to 50 μ g/mL. The bound percentage of the desacetyl metabolite was 16 to 32 %, which is approximately half of the parent compound. At a concentration of 100 μ g/mL in serum, only a small percentage of both the parent compound and its metabolite was bound; most probably the portion of the protein molecules which binds them is saturated at this concentration.

TOXICOLOGY

Acute Toxicity

In animal studies, cefotaxime has shown to be well tolerated, with a favourable therapeutic index. The lethality of cefotaxime in the mouse, rat, dog, and rabbit are listed in the table below.

COMPARATIVE ACUTE TOXICITY OF CEFOTAXIME IN LABORATORY ANIMALS

Species	Route	Male	Female
Mouse	IV	8700	8350
	IP	10 100	11 000
	SC	14 000	12 950
	PO	>20 000	
7-day old neonate	SC	6300	6100
Rat	IV	7000	7000
	IP	10 200	10 400
	SC	18 400	19 400
	PO	>20 000	
7-day old neonate	IP	>7000	
	SC	7200	7000
Dog	IV	>1000	
	IM	>716	
Rabbit	IV	>300	

There were no significant differences in sex or species. Cefotaxime was found to be approximately twice as toxic for newborns as it was for adults. The LD₅₀ of the desacetyl derivative of cefotaxime was determined in mice and found to be 9300 mg/kg in males and 6900 in females. Common signs of toxicity were clonic and tonic convulsions, dyspnea, hypothermia, and cyanosis.

Short-term Toxicity

In a 6-day acute toxicity study, cefotaxime was given intravenously to 3 groups of beagle dogs, each consisting of 2 males and 2 females at doses of 500 mg/kg for 2 days followed by 100 mg/kg for 4 days; and in a second group, 1000 mg/kg for 2 days followed by 250 mg/kg for 4 days. A third group of 4 dogs receiving physiological saline under the same conditions served as control. The results of biochemical tests were unremarkable although there were transient increases in urea and SGPT in a few treated males and in SGPT and alkaline phosphatase in 2 treated females.

At autopsy, microscopic examinations revealed superficial hemorrhages in the urethra of one high dose male and a similar finding in the bladder of a female of the same group. The hemorrhages were the apparent result of catheterization. The other high dose male has a scar on the kidney and two scars on the bladder. Histological examination of the livers showed a few areas of Kupffer cell hyperplasia in all treated males. A male and female of the high dose group had an abundance of glycogen in the hepatic parenchyma. Microscopic examination of the kidneys showed slightly dilated proximal convoluted tubules without epithelial changes in one male from each of the treated groups. Inflammatory and histocystic cells were noted in the kidneys of one male from both treated groups.

Long-term Toxicity (30 days and 13 weeks)

The long-term toxicity of cefotaxime was investigated in 3 groups of 17 rats each of both sexes receiving single daily subcutaneous doses of 300, 1000, and 3000 mg/kg for 1 month. Dilation of the cecum with inflammatory changes in the subcutaneous tissue at the sites of injection occurred even with the lowest dose. Dilation of the cecum, inflammatory changes at the injection sites accompanied by histopathological changes of the spleen and bone marrow, and tubular changes of the kidneys were observed in the group that received 1000 mg/kg. These changes were seen infrequently and had a slight degree of severity.

At the highest dose level (3000 mg/kg), there was dilation of the cecum and extensive subcutaneous hemorrhage at the injection sites. Secondary to the hemorrhagic and inflammatory changes were an increase in neutrophils and a decrease in red blood cell count, hematocrit and hemoglobin values. Lymphoid hyperplasia of the spleen and increased erythropoiesis in the bone marrow was also observed. Correspondingly, spleen weights were increased. After two weeks of reversal of treatment, these changes were reduced toward control values. Fragments of epithelial cell and amorphous salts were observed in the urine sediment of these animals. Kidney weights were increased in all females. Under microscopic examination, the kidneys were found to have dilated tubules and eosinophilic granular material in the proximal tubular epithelial cells.

In another study, cefotaxime was given under the same conditions to 3 groups of 15 rats each of both sexes at dose levels of 400, 800 and 1600 mg/kg/day for 13 weeks. Different parameters such as urinalysis, hematology, clinical chemistry and post-mortem examination of macroscopic and microscopic examination of lesions showed similar results as observed above.

The intravenous toxicity of cefotaxime was studied in 4 groups of 15 male and 15 female rats who received 0 to 1000 mg/kg/day in the caudal tail vein for one month. Cefotaxime administration caused neither remarkable changes in behaviour nor fatal cases in any of the treatment groups. Animals given the highest dose of 1000 mg/kg squeaked, tried to escape from the drug injection and developed inflammatory changes.

In the hematological tests, plasma recalcification time and prothrombin time were slightly shorter and the platelet count was decreased to a slight degree in the high dose rats in both sexes although these changes were not statistically significant. Autopsies of both males and females exhibited dose-dependent dilation of the cecum with retention of contents. In some of these cases, hemorrhage, inflammatory changes and attenuation of the wall of the cecum were observed microscopically. There were no spleen abnormalities except that lymphoid hyperplasia was observed in all of the drug-treated and control groups. However, in another study done under the same conditions, dose-related increases in spleen weights were reported. Histologically, the spleens of some of the animals treated with 100 or 300 mg/kg for 30 days were observed to have a moderate degree of white pulp activation.

The long-term intravenous and intramuscular toxicity of cefotaxime was further investigated in groups of 3 male and 3 female beagle dogs treated with doses ranging from 0 to 300 mg/kg/day for 30 consecutive days. When injected intravenously at 300 mg/kg/day, all dogs salivated profusely and showed clear nasal discharge. In dogs, the weight of the kidneys was increased. On

e male and all 3 females of the high dose group had hyperemia with slight edema in the cortical areas of the kidneys.

Hemorrhage and hemorrhagic residues were seen at the site of injection. Cefotaxime when given intramuscularly at doses of 72 or 179 mg/kg/day caused pain at the site of injection in a few animals. The intensity of the lesions at the site of injection and the frequency of their occurrences appear to be dose-related. Diarrhea was also noted in several dogs treated with cefotaxime at these doses.

In another study, cefotaxime was injected intravenously to beagle dogs (3 dogs/sex/group) at doses of 500, 1000 and 1500 mg/kg for 13 weeks. The mid and high-dose dogs salivated during the injection of the compound and occasionally had soft stools. At week 11, one female treated with 1500 mg/kg/day showed signs of anemia and when palpated, there was some evidence of a hemorrhagic disorder in the area of the spleen. The hemograms were consistent with an acute hemorrhage. Renal lesions graded minimal to slight were reported to occur in all drug groups but not in all dogs. Some dogs treated with 1000 and 1500 mg/kg/day showed a slight increase of extra medullary hematopoiesis in the spleens. In precapsular lymph nodes, an increase of focal lymphadenitis and erythrophagocytosis was seen in treated dogs. In male dogs, the lymph nodes showed increased activity of the germinal centres and hyperplasia of medullary plasmacytes.

Groups of 4 male and 4 female beagle pups received subcutaneous injections of cefotaxime in doses of 0 to 1500 mg/kg/day for 30 consecutive days. A dose-related response to pain, both in intensity and duration was observed. Post-mortem examinations revealed hemorrhage and edema at the injection site.

The long-term toxicity of intravenously administered cefotaxime was compared with that of cephaloridine and cephalothin in 6 groups of 3 male and 3 female rabbits treated daily for 30 days. Cefotaxime doses ranged from 0 to 120 mg/kg/day while cephaloridine and cephalothin were given at the daily dose of 120 mg/kg/day. In the cefotaxime group, one rabbit died at 30 mg/kg, 3 died at 60 mg/kg and 2 died at 120 mg/kg. Two rabbits in the cephaloridine group and one rabbit in the cephalothin group died. Diarrhea was observed in all treated groups. Neither cefotaxime nor cephalothin produced microscopic lesions. Cephaloridine produced myocardial necrosis in two rabbits.

Chronic Toxicity

The chronic toxicity of cefotaxime was investigated in rats and dogs over a period of 6 months.

Groups of 25 male and female rats received subcutaneous injections of cefotaxime in doses of 0, 40, 100, and 250 mg/kg/day for 7 days per week for 6 months. In general, chronic administration of cefotaxime for 6 months was well tolerated. Both female and male rats treated with 250 mg/kg/day showed slight and transient depression of body weight gain. Local tolerance reactions were noted in animals treated with 100 or 250 mg/kg from the third week to the end of the study. Microscopic examination of these tissues taken from the high dose animals showed marked inflammatory subcutaneous sclerosis often accompanied by the presence of hematomas and muscular atrophy.

One male treated with 250 mg/kg had to be sacrificed at 4 months of treatment because of sudden deterioration of its general condition. Histopathological examination revealed ulceration of the stomach mucosa, congestion of the liver and subcapsular interstitial scar in the kidney. Otherwise, there was no mortality in any of the groups.

The chronic toxicity of cefotaxime was further examined in dogs (4 animals/sex/group) when given intramuscularly at doses of 0, 40, 100 or 250 mg/kg/day 7 days a week for 26 weeks.

Reaction of pain was observed in all dogs in the highest dosage groups immediately following the injection. Histopathologic lesions at the injection sites showed a dose-related inflammatory response. No dogs died during the treatment. Numerous variations in hematology, coagulation and biochemical values were observed in individual animals. The variations were, however, within normal limits and the distribution in the two groups did not suggest an effect of the compound.

Fertility and Reproduction

Cefotaxime was administered intravenously in doses of 0, 100, 400, and 2000 mg/kg/day to groups of 22-24 male mice for 9 weeks prior to and including mating and to groups of 23-24 females for 2 weeks before mating and through day 6 of gestation. Under these conditions, the copulation and conception rate in the treated groups was comparable to those in the control group.

Treated groups did not differ from controls in the number of corpora lutea, resorptions, and live and dead fetuses. Body and placental weights, crown-rump lengths and sex ratio of the live fetuses from treated females corresponded with those found in the control group. The live fetuses at each dosage level showed no external, visceral or skeletal abnormalities considered to be related to the administration of the compound.

In a similar study performed in rats with 20-25 animals/sex/group, cefotaxime in doses of 0, 40, 100, or 250 mg/kg/day did not alter the sexual behaviour and reproductive function of the parents or the offspring.

Peri- and Post-Natal Behaviour

Two perinatal and postnatal studies were conducted with cefotaxime in 104 mated rats. In the first study, dosage levels of 150, 300 and 600 mg/kg were administered by intravenous injection twice daily at a minimum of 6 hours apart beginning on the 15th day of gestation and continuing throughout gestation and lactation.

No effects attributable to treatment with cefotaxime were observed on maternal appearance, behaviour, survival, fertility, length of gestation or number of live and nonviable pups. Maternal body weights were comparable during the gestation and lactation periods of cefotaxime-treated groups and the control groups with the exception of slightly reduced body weight gains in the 1200 mg/kg/day treated rats during the first 5 days of treatment and days 12 through 21 of lactation. Reduced mean pup body weights were noted in this group at birth through weaning.

No other biologically meaningful effects were noted from intravenous injection of cefotaxime at 1200 mg/kg/day or less during the latter portion of gestation through weaning.

Under a similar protocol, cefotaxime was given intramuscularly to rats in doses of 0, 40, 100, or 250 mg/kg/day. At these dose levels, no effects of cefotaxime were observed on the peri- and postnatal behaviour of the mothers and the general condition and viability of the offspring.

Teratology

Cefotaxime was administered intravenously in doses of 300, 600, and 1200 mg/kg/day to 20-23 pregnant mice, and to pregnant rats intravenously (300, 600, and 1200 mg/kg/day) or intramuscularly (40, 95, or 210 mg/kg/day) from day 6 through day 15 or 18 of gestation. No findings indicative of a drug-related teratogenic effect was noted in any of the fetuses at necropsy or during the visceral and skeletal examination. On the basis of these studies, cefotaxime was not considered embryotoxic or teratogenic when administered parenterally in mice and rats at levels up to 1200 mg/kg/day.

The teratogenic effect of cefotaxime was further studied in pregnant rabbits treated with daily doses of 25, 50, and 90 mg/kg intramuscularly for sequential periods of 4 to 7 days throughout the phase of embryogenesis. Maternal toxicity and embryotoxicity were recorded in groups dosed with 50 mg/kg and higher. Lower fetal weights were recorded in the groups dosed with 90 mg/kg/day and a few malformations or simple abnormalities appeared in all groups, including controls. Rabbits are particularly sensitive to cephalosporin antibiotics and are therefore inappropriate species for testing the reproductive and teratogenic effects of cefotaxime.

Mutagenicity Studies

The mutagenic effects of cefotaxime were investigated using the micronucleus test in mice and the Ames test in bacterial strains. No mutagenicity could be attributed to cefotaxime using these two standard methods.

Carcinogenicity

Long term studies in animals have not been performed to evaluate the carcinogenic potential of cefotaxime.

Nephrotoxicity

The potential nephrotoxicity of cefotaxime was compared to that of cephaloridine and cephalothin in rabbits (2 male and 2 females per group). Daily intramuscular doses of 220 mg/kg of cefotaxime, 200 mg/kg of cephaloridine and 190 mg/kg of cephalothin were administered to the groups for seven consecutive days. All three antibiotics induced emaciation in some animals and death of one rabbit in each treated group. Only in the animals treated with cephaloridine did the histological examination reveal tubular necrosis. No morphological substance-induced organ changes were detected in the rabbits treated with cefotaxime or cephalothin.

Furosemide, a potent diuretic, has been shown to enhance the nephrotoxicity of cephaloridine in animals. Studies were conducted in mice and rats to evaluate the effect on the renal function and renal histology of a single parenteral dose of 20 mg/kg of furosemide given 15 minutes before the injection of cefotaxime. Cefotaxime was administered to mice in doses of 2000 or 4000

mg/kg and to rats in doses of 2500 or 5000 mg/kg. Microscopic examination of the kidneys revealed some dilated tubules in the cortex and the medulla and some hyalin casts in control and all treated groups regardless of furosemide administration.

The nephrotoxicity of the combined administration of cefotaxime (1000 mg/kg/day i.v.) with gentamicin (30 mg/kg/day i.m.) or furosemide (100 mg/kg/day p.o.) was studied in groups of 16 female rats for 28 consecutive days. Single treatments with each drug, alone or in combination with cefotaxime did not produce death nor abnormalities in behaviour or appearance, nor did they affect body weight gain or food consumption. The main histopathological findings were as follows: occurrence of eosinophilic material (slight degeneration) in the epithelial cells of the proximal convoluted tubules, considered to be due to a change in the lysosomes, in the group given cefotaxime alone; interstitial inflammation and slight focal necrosis in the proximal tubules in rats injected only with gentamicin; and calcification of the distal convoluted tubules in animals administered furosemide alone. The concurrent administration of cefotaxime with gentamicin or furosemide produced combinations of the above described changes, each of which was not enhanced either in incidence or in extent.

Tolerance Studies

The local intravenous tolerance of cefotaxime was investigated in rats and dogs. Rats (15 animals/sex/group) injected intravenously in the caudal vein daily for 30 days with cefotaxime at doses of 125, 500 and 1000 mg/kg in physiological saline and those being used as controls showed a slight but dose-related degeneration of the epidermis, hemorrhage, perifollicular edema and inflammatory cell infiltration of the dermis and subcutaneous tissues. In dogs, however, the intravenous tolerance was not dose-related and did not differ from that of the controls. The minimal lesions observed at the injection sites following a 13 week administration of 0 to 1500 mg/kg/day were interpreted as being caused by the trauma of repeated i.v. injections rather than by cefotaxime itself.

The local intramuscular tolerance of cefotaxime was compared with that of cephaloridine in 2 groups of 10 male rats given a single injection of 100 µg per rat. Cefotaxime caused only minor and transient local tissue damage - necrotic areas, fragmentation of muscle fibres and inflammation - while similar doses of cephaloridine produced more severe and persistent damage.

The local intramuscular tolerance of 1000 mg/kg of cefotaxime was investigated in groups of three male and female rabbits when given in a single injection with or without 1% lidocaine. One rabbit in each group died of diarrhea and no substance-induced organ lesions were observed at the end of a three week follow-up period. This study showed that the tolerance to 1000 mg/kg of cefotaxime in rabbits was not affected by the administration in a 1% lidocaine solution.

The sub-occipital tolerance of cefotaxime was compared with that of cephaloridine when given as a single sub-occipital injection to groups of 10 rats at doses ranging from 2.5 to 19 mg/kg. Doses of 2.5 and 5 mg/kg of cephaloridine and 19 mg/kg of cefotaxime caused prostration, respiratory impairment, hyperventilation, tremors, and convulsions. At each of these dosage levels, 40-60% of the animals per group died a few minutes following the injections. Doses of

2.5, 5, and 9.5 mg/kg of cefotaxime and 1.25 mg/kg of cephaloridine were satisfactorily tolerated.

To investigate the intrathecal tolerance of cefotaxime, 50 mg was administered as a single dose through the foremen magnum to two male and female beagle dogs. All dogs treated with cefotaxime showed slight tetanoid convulsions for about one hour towards the end of anesthesia. Histological examinations did not reveal any compound-related impairment of the central nervous system, the spinal cord or meninges.

The renal tolerance of cefotaxime was further compared with that of cephaloridine in groups of 2 male and 2 female beagle dogs when given as a single 1000 mg/kg intravenous injection. In contrast to cephaloridine, cefotaxime caused only a slight and transient reduction of PAH clearance. Creatinine clearance remained unchanged and the urinary output was not disturbed at any time.

Combination LD₅₀ Study

The toxicity of combinations of cefotaxime and gentamicin when studied in rats did not appear very different from the toxicity exhibited by the individual components.

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