Cefoperazone Sodium

(BANM, USAN, rINNM)

Cefoperazon sodná sůl; Cefoperazon sodowy; Cefoperazona sódica; Céfopérazone sodique; Cefoperazonnatrium; Cefoperazon-nátrium; Cefoperazono natrio druska; Cefoperazonum natricum; CP-52640-2; CP-52640 (anhydrous cefoperazone); CP-52640-3 (cefoperazone dihydrate); Kefoperatsoninatrium; Natrii Cefoperazonum; Sefoperazon Sodyum; T-1551 (cefoperazone or cefoperazone sodium). Sodium (7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-2-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate.

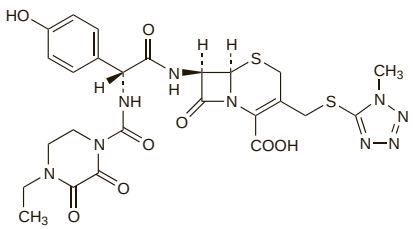
Натрий Цефоперазон

$C_{25}H_{26}N_9NaO_8S_2$ = 667.6.

CAS — 62893-19-0 (cefoperazone); 62893-20-3 (cefoperazone sodium).

ATC — J01DD12.

ATC Vet — QJ01DD12.



(cefoperazone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Cefoperazone Sodium). A white or slightly yellow, hygroscopic, powder. If crystalline it exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 25% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 2° to 8°. Protect from light.
USP 31 (Cefoperazone Sodium). A white to pale buff crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; insoluble in acetone, in ether, and in ethyl acetate. pH of a 25% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. As with most beta lactams, admixture of cefoperazone sodium with aminoglycosides is not recommended because of the potential for inactivation of either drug.

There have been reports of incompatibility with other drugs including diltiazem,[1] doxorubicin,[2] pentamidine,[3] perphenazine,[4] pethidine,[5] promethazine,[6] and remifentanil.[7]

1. Gayed AA, *et al.* Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52:** 516–20.
2. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
3. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.
4. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.
5. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
6. Scott SM. Incompatibility of cefoperazone and promethazine. *Am J Hosp Pharm* 1990; **47:** 519.
7. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Like cefotaxime (p.228), cefoperazone has the potential for colonisation and superinfection with resistant organisms. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of cefoperazone; diarrhoea may occur more often.

Cefoperazone contains an *N*-methylthiotetrazole sidechain, a structure associated with hypoprothrombinaemia. Hypoprothrombinaemia has been reported in patients treated with cefoperazone and has rarely been associated with bleeding episodes. Prothrombin time should be monitored in patients at risk of hypoprothrombinaemia and vitamin K used if necessary.

Sodium content. Each g of cefoperazone sodium contains about 1.5 mmol of sodium.

Interactions

As for Cefamandole, p.221.

Unlike many other cephalosporins, probenecid has no effect on the renal clearance of cefoperazone.

Antimicrobial Action

Cefoperazone has antimicrobial activity similar to that of ceftazidime (p.234), although it is slightly less active against some Enterobacteriaceae. It has good activity against *Pseudomonas aeruginosa*, but is less active than ceftazidime.

Cefoperazone is more susceptible than cefotaxime to hydrolysis by certain beta-lactamases.

Activity, particularly against Enterobacteriaceae and *Bacteroides* spp. has been enhanced in the presence of the beta-lactamase inhibitor sulbactam; resistant *Ps. aeruginosa* are not sensitive to the combination.

◊ References.

1. Fass RJ, *et al.* In vitro activities of cefoperazone and sulbactam singly and in combination against cefoperazone-resistant members of the family Enterobacteriaceae and nonfermenters. *Antimicrob Agents Chemother* 1990; **34:** 2256–9.
2. Clark RB, *et al.* Multicentre study on antibiotic susceptibilities of anaerobic bacteria to cefoperazone-sulbactam and other antimicrobial agents. *J Antimicrob Chemother* 1992; **29:** 57–67.

Pharmacokinetics

Cefoperazone is given parenterally as the sodium salt. With intramuscular doses equivalent to cefoperazone 1 or 2 g, peak plasma concentrations of 65 and 97 micrograms/mL have been reported after 1 to 2 hours. The plasma half-life of cefoperazone is about 2 hours, but may be prolonged in neonates and in patients with hepatic or biliary-tract disease. Cefoperazone is 82 to 93% bound to plasma proteins, depending on the concentration.

Cefoperazone is widely distributed in body tissues and fluids, although penetration into the CSF is generally poor. It crosses the placenta, and low concentrations have been detected in breast milk.

Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Urinary excretion is primarily by glomerular filtration. Up to 30% of a dose is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found only rarely *in vivo*.

Uses and Administration

Cefoperazone is a third-generation cephalosporin antibiotic used similarly to ceftazidime (p.235) in the treatment of susceptible infections, especially those due to *Pseudomonas* spp. It is not recommended for the treatment of meningitis because of poor penetration into the CSF.

Cefoperazone is given as the sodium salt by deep intramuscular injection or intravenously by intermittent or continuous infusion. Doses are expressed in terms of the equivalent amount of cefoperazone; 1.03 g of cefoperazone sodium is equivalent to about 1 g of cefoperazone. The usual dose is 2 to 4 g daily in 2 divided doses. In severe infections, up to 12 g daily in 2 to 4 divided doses may be given.

For details of dosage in patients with hepatic and renal impairment, see below.

If cefoperazone is used with an aminoglycoside, the drugs should be given separately.

Cefoperazone has also been given with the beta-lactamase inhibitor sulbactam.

Administration in hepatic and renal impairment. In general, the dose of cefoperazone should not exceed 4 g daily in patients with liver disease or biliary obstruction or 1 to 2 g daily in those with both hepatic and renal impairment; if higher doses are used plasma concentrations of cefoperazone should be monitored.

Preparations

USP 31: Cefoperazone for Injection; Cefoperazone Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefobid†; ***Austria:*** Cefobid; ***Braz.:*** Cefazone†; Neoperazona†; ***Chile:*** Cefobid; ***Cz.:*** Cefobid; ***Hong Kong:*** Cefobid; ***Hung.:*** Cefobid; ***India:*** Cefomycin; Magnamycin; ***Indon.:*** Bifotik; Cefobid; Cefophar; Ceropid; Cerozon; Ferzobat; Logafox; Stabixin; ***Ital.:*** Bioperazone; Cefoneg†; Cefoper; Dardum; Farecef; Ipazone†; Novobiocyl†; Tomabef†; Zonceft; ***Jpn:*** Cefobid†; Cefoperazin; ***Malaysia:*** Cefobid; Medocef; Shinfomycin; ***Mex.:*** Cefobid; ***Philipp.:*** Bactizon; ***Pol.:*** Biocefazon; Cefobid; Dardum; ***Rus.:*** Cefobid (Цефобид); Medocef (Медоцеф); ***Singapore:*** Cefobid; Cefozone; Dardum; ***Spain:*** Cefobid†; ***Thai.:*** Cefobid; Cefozone†; Medocef; ***Turk.:*** Cefobid; ***USA:*** Cefobid†; ***Venez.:*** Cefobid†; Ortosep†.

Multi-ingredient: ***Arg.:*** Sulperazon†; ***Chile:*** Sulperazon; ***Cz.:*** Sulperazon; ***Hong Kong:*** Sulperazon; ***India:*** Lactagard; Sulbacef; Zosul; ***Indon.:*** Fosular; Stabactam; Sulperazon; ***Malaysia:*** Sulperazon; ***Philipp.:*** Sulperazone; ***Pol.:*** Sulperazon; ***Rus.:*** Sulcef (Сульцеф); Sulperason (Сульперазон); ***Thai.:*** Cebactam; Cefper; Sulcef; Sulperazon; ***Turk.:*** Primasef; Sulperazon; ***Venez.:*** Sulperazon.

Ceforanide *(BAN, USAN, rINN)*

BL-S786; Ceforanida; Céforanide; Ceforanidum. 7-[2-(α-Amino-*o*-tolyl)acetamido]-3-(1-carboxymethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

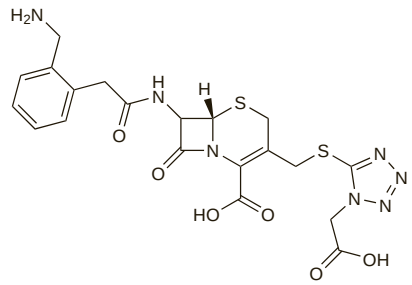
Цефоранид

$C_{20}H_{21}N_7O_6S_2$ = 519.6.

CAS — 60925-61-3.

ATC — J01DC11.

ATC Vet — QJ01DC11.



Pharmacopoeias. In *US*.
USP 31 (Ceforanide). A white to off-white powder. Practically insoluble in water, in chloroform, in ether, and in methyl alcohol; very soluble in 1N sodium hydroxide. pH of a 5% suspension in water is between 2.5 and 4.5. Store in airtight containers.

Profile

Ceforanide is a second-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p.220), although it is reported to be less active *in vitro* against some bacteria, including staphylococci and *Haemophilus influenzae*. It is used in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the lysine salt ($C_{26}H_{35}N_9O_8S_2$ = 665.7) but doses are expressed in terms of the equivalent amount of ceforanide; 1.28 g of ceforanide lysine is equivalent to about 1 g of ceforanide. It is given by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion. The usual adult dose is 1 to 2 g every 12 hours. Children may be given 20 mg/kg daily in 2 divided doses. For surgical infection prophylaxis, a dose of 1 to 2 g intravenously 1 hour before surgical incision is used in adults.

Ceforanide contains a substituted *N*-methylthiotetrazole sidechain, a structure associated with hypoprothrombinaemia and alcohol intolerance. Probenecid does not affect the renal excretion of ceforanide.

◊ References.

1. Campoli-Richards DM, *et al.* Ceforanide: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1987; **34:** 411–37.

Preparations

USP 31: Ceforanide for Injection.

Proprietary Preparations (details are given in Part 3)

Belg.: Precef†; ***Gr.:*** Radacef.

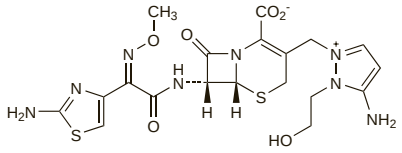
Cefoselis Sulfate *(rINNM)*

Céfosélis, Sulfate de; Cefoselis Sulphate; Cefoselisi Sulfas; FK-037; Sulfato de cefoselís. (−)-5-Amino-2-({(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl}methyl)-1-(2-hydroxyethyl)pyrazolium hydroxide, inner salt, 7²-(*Z*)-(*O*-methyloxime) sulfate.

Цефозелиса Сульфат

$C_{19}H_{22}N_8O_6S_2$, H_2SO_4 = 620.6.

CAS — 122841-10-5 (cefoselis); 122841-12-7 (cefoselis sulfate).



(cefoselis)

Profile

Cefoselis sulfate is a cephalosporin antibacterial that has been used in the treatment of susceptible bacterial infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Winceft.

Cefotaxime Sodium *(BANM, USAN, rINNM)*

Cefotaksimo natrio druska; Cefotaksym sodowy; Cefotaxim sodná sůl; Cefotaxima sódica; Céfotaxime sodique; Cefotaximnatrium; Cefotaxim-nátrium; Cefotaximum natricum; CTX; HR-756; Kefotaksiiminatrium; Natrii Cefotaximum; RU-24756; Sefotaksim Sodyum. Sodium (7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

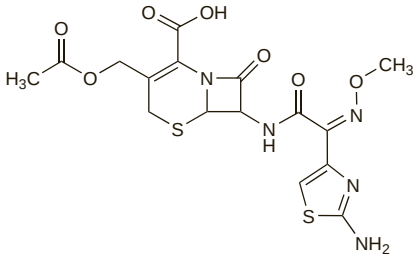
Натрий Цефотаксим

$C_{16}H_{16}N_5NaO_7S_2$ = 477.4.

CAS — 63527-52-6 (cefotaxime); 64485-93-4 (cefotaxime sodium).

ATC — J01DD01.

ATC Vet — QJ01DD01.



(cefotaxime)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Cefotaxime Sodium). A white or slightly yellow, hygroscopic, powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH of between 4.5 and 6.5. Store in airtight containers. Protect from light.
USP 31 (Cefotaxime Sodium). An off-white to pale yellow crystalline powder. Freely soluble in water; practically insoluble in organic solvents. pH of a 10% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate. Licensed product information recommends that it should be given separately from aminoglycosides.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219. Arrhythmias have been associated with rapid bolus dosage through a central venous catheter in a few cases.

The broad-spectrum third-generation cephalosporins have the potential for colonisation and superinfection with resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Candida*, and enterococci, at various sites in the body, although the incidence has generally been low with cefotaxime. Changes in bowel flora are a predisposing factor and have been more marked with cefoperazone and ceftriaxone, possibly because of their greater biliary excretion. Pseudomembranous colitis, associated with *Clostridium difficile* infection, may occasionally be seen with any of the third-generation cephalosporins.

◊ Reviews on adverse effects associated with third-generation cephalosporins.

1. Neu HC. Third generation cephalosporins: safety profiles after 10 years of clinical use. *J Clin Pharmacol* 1990; **30:** 396–403.
2. Fekety FR. Safety of parenteral third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 38S–44S.

Antibiotic-associated colitis. It has been suggested[1] that cefotaxime is associated with an increased risk of *Clostridium difficile* diarrhoea in elderly patients; however, the manufacturer[2] has disputed this, arguing that cefotaxime compares favourably with alternative third-generation cephalosporins.

1. Impallomeni M, *et al.* Increased risk of diarrhoea caused by Clostridium difficile in elderly patients receiving cefotaxime. *BMJ* 1995; **311:** 1345–6.
2. Rothschild E, *et al.* Risk of diarrhoea due to Clostridium difficile during cefotaxime treatment. *BMJ* 1996; **312:** 778.

Breast feeding. Although cefotaxime is excreted in breast milk in small amounts,[1] no adverse effects have been observed in breast-fed infants whose mothers were receiving cefotaxime, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Sodium content. Each g of cefotaxime sodium contains about 2.09 mmol of sodium.

Interactions

As for many cephalosporins, probenecid reduces the renal clearance of cefotaxime, resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite.

Antibacterials. The total body clearance of cefotaxime has been reduced in patients with normal and reduced renal function by the ureidopenicillins *azlocillin*[1] or *mezlocillin*.[2] Doses of cefotaxime may need to be reduced if either of these penicillins is being given. Encephalopathy with focal motor status and generalised convulsions have been reported in a patient with renal failure given cefotaxime and high doses of azlocillin.[3]

1. Kampf D, *et al.* Kinetic interactions between azlocillin, cefotaxime, and cefotaxime metabolites in normal and impaired renal function. *Clin Pharmacol Ther* 1984; **35:** 214–20.
2. Rodondi LC, *et al.* Influence of coadministration on the pharmacokinetics of mezlocillin and cefotaxime in healthy volunteers and in patients with renal failure. *Clin Pharmacol Ther* 1989; **45:** 527–34.
3. Wroe SJ, *et al.* Focal motor status epilepticus following treatment with azlocillin and cefotaxime. *Med Toxicol* 1987; **2:** 233–4.

Antimicrobial Action

Cefotaxime is a third-generation cephalosporin. It has a bactericidal action similar to cefamandole, but a broader spectrum of activity. It is highly stable to hydrolysis by most beta-lactamases and has greater activity than first- or second-generation cephalosporins against Gram-negative bacteria. Although cefotaxime is generally considered to have slightly less activity than first-generation cephalosporins against Gram-positive bacteria, many streptococci are very sensitive.

Desacetylcefotaxime is an active metabolite of cefotaxime and there may be additive or synergistic effects against some species.

Spectrum of activity. Among Gram-negative bacteria, cefotaxime is active *in vitro* against many Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., both indole-positive and indole-negative *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Other susceptible Gram-negative bacteria, including penicillin-resistant strains, are *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis*. *Brucella melitensis* is also reported to be moderately sensitive. Some strains of *Pseudomonas* spp. are moderately susceptible to cefotaxime, but most are resistant. Desacetylcefotaxime is active against many of these Gram-negative bacteria, but not against *Pseudomonas* spp.

Among Gram-positive bacteria, cefotaxime is active against staphylococci and streptococci. *Staphylococcus aureus*, including penicillinase-producing strains but not meticillin-resistant *Staph. aureus*, is sensitive. *Staph. epidermidis* is also sensitive but penicillinase-producing strains are resistant. *Streptococcus agalactiae* (group B streptococci), *Str. pneumoniae*, and *Str. pyogenes* (group A streptococci) are all very sensitive although truly penicillin-resistant pneumococci are apparently not sensitive. Enterococci and *Listeria monocytogenes* are resistant.

Cefotaxime is active against some anaerobic bacteria. *Bacteroides fragilis* may be moderately sensitive, but many strains are resistant; synergy has been demonstrated with desacetylcefotaxime *in vitro*. *Clostridium perfringens* is sensitive, but most *Cl. difficile* are resistant.

Other organisms sensitive to cefotaxime include the spirochaete *Borrelia burgdorferi* and *Haemophilus ducreyi*.

Activity with other antimicrobials. In addition to possible synergy or additive effects with desacetylcefotaxime, the activity of cefotaxime may be enhanced by aminoglycosides such as gentamicin; synergy has been demonstrated *in vitro* against Gram-negative bacteria including *Pseudomonas aeruginosa*. There have also been reports of enhanced activity *in vitro* with other antibacterials including fosfomycin and ciprofloxacin and variable results with penicillins.

Resistance may develop during treatment with cefotaxime due to derepression of chromosomally mediated beta-lactamases, and has been reported particularly in *Enterobacter* spp., with multiresistant strains emerging during treatment. This type of resistance has also developed in other bacteria including *Citrobacter*, *Serratia*, and *Pseudomonas* spp. Another mechanism of cefotaxime resistance is the development of plasma-mediated, extended-spectrum beta-lactamases, and this has occurred in *Klebsiella* spp. and also other Enterobacteriaceae. Resistance in *Str. pneumoniae* is due to the production of altered penicillin-binding proteins.

◊ References to the antimicrobial activity of cefotaxime and other third-generation cephalosporins, including the problem of bacterial resistance.

1. Neu HC. Pathophysiologic basis for the use of third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 3S–11S.
2. Chow JW, *et al.* Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115:** 585–90.
3. Sanders CC. New β-lactams: new problems for the internist. *Ann Intern Med* 1991; **115:** 650–1.
4. Thomson KS, *et al.* High-level resistance to cefotaxime and ceftazidime in Klebsiella pneumoniae isolates from Cleveland, Ohio. *Antimicrob Agents Chemother* 1991; **35:** 1001–3.
5. Piddock LJV, *et al.* Prevalence and mechanism of resistance to 'third-generation' cephalosporins in clinically relevant isolates of Enterobacteriaceae from 43 hospitals in the UK, 1990-1991. *J Antimicrob Chemother* 1997; **39:** 177–87.
6. Gums JG, *et al.* Differences between ceftriaxone and cefotaxime: microbiological inconsistencies. *Ann Pharmacother* 2008; **42:** 71–9.

Pharmacokinetics

Cefotaxime is given by injection as the sodium salt. It is rapidly absorbed after intramuscular injection and mean peak plasma concentrations of about 12 and 20 micrograms/mL have been reported 30 minutes after doses of 0.5 and 1 g of cefotaxime, respectively. Immediately after intravenous injection of 0.5, 1, or 2 g of cefotaxime, mean peak plasma concentrations of 38, 102, and 215 micrograms/mL, respectively, have been achieved with concentrations ranging from about 1 to 3 micrograms/mL after 4 hours. The plasma half-life of cefotaxime is about 1 hour and that of the active metabolite desacetylcefotaxime about 1.5 hours; half-lives are increased in neonates and in patients with severe renal impairment, especially those of the metabolite, and a reduction in dosage may be necessary. The effects of liver disease on clearance of cefotaxime and its metabolite have been variable, but in general dosage adjustment has not been considered necessary. About 40% of cefotaxime is reported to be bound to plasma proteins.