Ceftriaxone: Indications, Mechanism of action, Dosage, Interactions and, Side Effects,

Ceftriaxone is a third generation cephalosporin antibiotic that is used in the treatment of bacterial infections caused by susceptible, usually gram-positive organisms.

Ceftriaxone has an invitro activity against gram positive and gram negative aerobic and anaerobic bacteria.

Mechanism of action of ceftriaxone

Ceftriaxone works by inhibiting mucopeptide synthesis in the bacterial cell wall.

Ceftriaxone has a broad-spectrum gram-negative activity and a lower efficacy against gram-positive organisms but higher efficacy against resistant organisms.

Ceftriaxone is stable against hydrolysis by a variety of beta lactamases including penicillinases and cephalosporinases and extended spectrum beta lactamases of gram-negative and gram-positive bacteria.

The bactericidal activity of ceftriaxone results from inhibiting cell-wall synthesis that is mediated by binding to 1 or more penicillin-binding proteins (PBPs) and exerting antimicrobial effect by interfering and interrupting the biosynthesis of peptidoglycan (major structural component of bacterial cell wall.

The beta lactam moiety of ceftriaxone binds to cerboxypeptidases, endopeptidases and transpeptidases in the bacterial cytoplasmic membrane. These enzymes are involved in the cell wall synthesis and cell division.

By binding to these enzymes, ceftriaxone results in the formation of defective cell walls and cell death of the susceptible bacteria because activity of cell-wall autolytic enzymes continues while cell-wall assembly is arrested

Resistance

Bacterial resistance to ceftriaxone may develop as a result of the following mechanisms:

- Hydrolysis by beta-lactamases that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- Bacterial efflux pumps.
- Outer membrane impermeability in Gram-negative organisms.
- Reduced affinity of penicillin-binding proteins for ceftriaxone.

Pharmacodynamics

Ceftriaxone is stable in a wide range of both gram-positive and gram-negative beta lactamases, including those which are able to hydrolyze advanced generation penicillin derivatives and other cephalosporins.

Resistance to ceftriaxone is encoded mainly in the production of the beta lactam hydrolyzing enzymes including carbapenemases and some ESBLs especially in Gram-negative organisms.

For gram positive organisms such as staphylococcus aureus and S pneumonia, acquired resistance is mainly encoded by cell wall target site allowances.

Pharmacokinetics

Ceftriaxone demonstrates nonlinear dose-dependent pharmacokinetics because its protein binding about 85% - 95% is bound to plasma protein depending on the concentration of ceftriaxone.

Mean peak plasma concentrations of about 40 to 80 micrograms/Ml have been reported 2-3 hours after administration of 0.5 to 1 gram intramuscularly.

Ceftriaxone has a VD of 6-14 L

The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 to 9 hours; it may be prolonged in neonates.

The half-life does not change more especially in patients with moderate renal impairment but it may be prolonged in severe renal failure especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body fluids and tissues.

It crosses both inflamed and non-inflamed meninges generally achieving therapeutic concentration in the CSF.

The excretion of ceftriaxone is mainly through the biliary tract, and no dosage adjustment is required in renal insufficiency.

It crosses the placenta and low concentration has been detected in breast milk. High concentration is achieved in bile.

About 40% to 65% of a dose of ceftriaxone is excreted unchanged in the urine principally by glomerular filtration, the remainder is excreted in the bile and is ultimately found in the feaces as unchanged drug and microbiologically inactive compounds.

Indications of ceftriaxone

Ceftriaxone is indicated in the management of the following infections in adults and children including neonates from birth

1. Bacterial meningitis
2. Community acquired pneumonia
3. Hospital acquired pneumonia

4. Acute otitis media
5. Intraabdominal infections
6. Complicated unrinary tract infections including pyelonephritis
7. Bone and joint infection
8. Complicated skin and soft tissue infection
9. Gornorrhea
10. Syphilis
11. Bacterial endocarditis
12. Ceftriaxone can also be used I the treatment ofacute exacebations of chronic obstructive pulmonary disease in adults
13. Disseminated lyme borreliosis (early stage ii) and late stage iii in adults and children including neonates from 15 days of age.
14. Preoperative prophylaxis of surgical site infections,
15. Management of neutropenic patients with ever that is suspected to be due to bacterial infections,

Ceftriaxone is used for treatment of meningitis, including meningitis caused by pneumococci, meningococci, H influenzae, and susceptible enteric gram-negative rods, but not by L monocytogenes.

Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin non-susceptible strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these
strains.

Meningitis caused by strains of pneumococci with penicillin MICs > 1 mcg/mL may not respond to ceftriaxone and therefore an addition of vancomycin is recommended.

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria could not fall within its spectrum.

Administration

For intramuscular administration 1 gram vial of ceftriaxone should be dissolved in 3.5ml of sterile water for injection or 1% Lidocaine Injection BP and the solution should be administered by deep intramuscular injection within the bulk of a relatively large muscle.

More than 1 gram of ceftriaxone should be injected at one site. Therefore dosages greater than 1gram should be divided and injected at more than one site.

As the solvent used is lidocaine, the resulting solution should never be administered intravenously

For intravenous administration,1 gram of ceftriaxone is dissolved in 10 ml of water for injections. The injection should be administered slowly for over 5 minutes, directly into the vein or as an infusion over at least 30 minutes.

An intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion.

In neonates, intravenous doses should be given over a duration of 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Ceftriaxone is contraindicated in neonates (? 28 days) if they require treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium. This is covered in details in the warning section.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

IV Incompatibilities

Ringers lactate solution at drug concentrations >10 mg/Ml.

Aminophylline, linezolid, metronidazole (at metronidazole 15 g/L with ceftriaxone 20 g/L; compatible at metronidazole 7.5 g/L with ceftriaxone 10 g/L), clindamycin, theophylline,

Calcium-containing drugs

Dosages

Adults and children above 12 years of age(=50 kgs)

For community acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, intra-abdominal infections and complicated urinary tract infections including pyelonephritis the dose is 1-2 grams daily.

For hospital acquired pneumonia, complicated skin infections, soft tissue infections, bone and joint infections the dosage is 6 grams once daily.

Management of acute neutropenic patients with fever that is suspected to be due to bacterial infections, bacterial endocarditis and bacterial meningitis the dosage is 2-4 grams per day.

Acute otitis media a single intramuscular injection of 1-2 grams is given.

Preoperative prophylaxis of surgical site infections 2 grams as a single dose

Gornorrhea 500 mg as a single intramuscular dose

Syphilis 500 to 1 gram once daily dose increased to 2 grams once daily for neurosyphyllis to 10-14 days

Disseminated lyme borreliosis a daily 2 gram dose is given for 10-14 days

Pelvic Inflammatory Disease

250 mg IM as single dose with doxycycline, with or without metronidazole for 14 days

Prosthetic Joint Infection

2 g IV q24hr for 2-6 weeks; continue treatment until clinical improvement observed and patient is afebrile for 48-72 h

The recommended treatment durations vary and national or local guidelines should be taken into consideration

Neonates and infants and children 15 days to 12 years (<50 kgs)

For children with body weight of 50 kilograms and below the usual adult dosage should be given