CHAPTER II

REVIEW OF CEFTRIAXONE

1. Physicochemical Properties (McEvoy, ed., 1994 ; The United States Pharmacopoeial Convention, Inc. 1995).

Ceftriaxone is a semisynthetic cephalosporin antibiotic. It contains an aminothiazolyl-acetyl side chain, with a methoxyimino group, at position 7 of the cephalosporin nucleus. The aminothiazolyl side chain enhances antibacterial activity and the methoxyimino group imparts stability against hydrolysis by many β-lactamases. Ceftriaxone also has and acidic enol in the triazine moiety at position 3 of the cephalosporin nucleus, which presumably is responsible for the long serum half-life of the drug. (Figure 1)

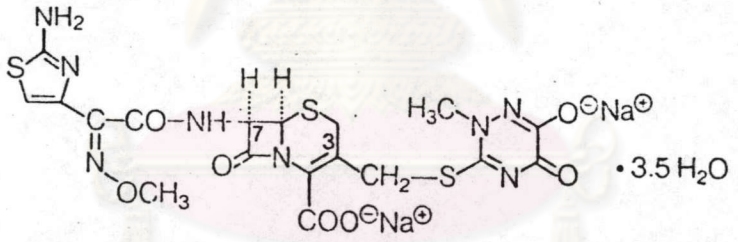

Figure 1 Chemical structure of ceftriaxone

Chemical name	:	5-Thia-1-azabicyclo [4.2.0]oct-2-ene-2-Carbaxylic acid, 7-[[(2-amino-4-thiazolyl) (methoxyimino) acetyl] amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl) thio] methyl]-, disodium salt,[6R-[6α,7β(Z)]]-, hydrate (2:7)
Empirical formula	:	$C_{18}H_{16}N_8Na_2O_7S_3 \bullet 3\ 1/2\ H_2O$
Molecular weight	:	661.61, anhydrous 598.56
Synonym	:	Ro 13-9904
Appearance	:	white to yellowish-orange crystalline powder
Solubility	:	400 mg/ml in water at 25°C ; 1 mg/ml in alcohol at 25°C
Acidity	:	pK_as of 3,3.2 and 4.1

1.1 Stability

Ceftriaxone sodium sterile powder should be stored at 25°C or lower and protected from light. However, it is unnecessary to protect reconstituted solutions of the drug from normal light. The frozen ceftriaxone sodium injection should be stored at a temperature not greater than -20°C.

Following reconstitution with 1% lidocaine hydrochloride injection (without epinephrine), solutions of the drug containing 100 mg/ml are stable for 24 hr. at room temperature or 10 days when refrigerated at 4°C, and solutions containing 250 mg/ml are stable for 24 hr. at room temperature or 3 days at 4°C (McEvoy, 1994)

2. Pharmacology

2.1 Mechanism of action

Ceftriaxone is usually bactericidal in action. The antibacterial activity of the drug results from inhibition of mucopeptide synthesis in the bacterial cell wall (McEvoy, 1994).

Base on the spectrum of activity, ceftriaxone is generally classified as a third generation cephalosporin.

2.2 In vitro activity

Ceftriaxone is generally less active in vitro against susceptible staphylococci than first generation cephalosporins but has an expanded spectrum of activity against gram-negative bacteria compared with first and second generation cephalosporins. In vitro on a weight basis, the activity of ceftriaxone against most susceptible organisms, include most Enterobacteriaceae, is approximately equal to that of cefotaxime or ceftizoxime.

Ceftriaxone is active in vitro against most gram-positive aerobic cocci including penicillinase-producing and nonpenicillinase-producing strains of Staphylococci and

some strains of Streptococci, but Staphylococci resistant to penicillinase-resistant penicillins and Enterococci are generally resistant to ceftriaxone. Ceftriaxone is also active in vitro against most gram-negative aerobic bacteria including Neisseria, Haemophilus, Enterobacteriaceae, Pseudomonas spp. and Acinetobacter. Ceftriaxone also has some activity in vitro against anaerobic bacteria including Actinomyces, some strains of Clostridium.

2.3 Resistant

Ceftriaxone is generally as stable as cefotaxime against inactivation by β-lactamase but less stable than moxalactam or cefoxitin.

Resistant strains of some organisms, including Enterobacter and Ps. aeruginosa, have developed during therapy with ceftriaxone because they posses inducible β-lactamases,that are appeared to inactivate β-lactam antibiotics by binding to the drug, which prevents them from binding to penicillin-binding proteins of the organisms.

3. Pharmacokinetics

Ceftriaxone was administered as ceftriaxone sodium, dosages and concentrations of the drug are expressed in terms of ceftriaxone.

Ceftriaxone exhibits nonlinear dose-dependent pharmacokinetics. Most pharmacokinetic parameters (except elimination half-life and the fraction excreted unchanged in urine) of total ceftriaxone (both protein-bound and unbound drug) are dose dependent and increase non linearly with increase in dosage. Pharmacokinetic parameters of free (unbound) ceftriaxone are not dose dependent and increase linearly with dosage.

Dose dependent changes in the pharmacokinetic parameters of ceftriaxone appearly occur because the drug exhibits concentration-dependent protein binding.

3.1 Absorption

Ceftriaxone is not appreciably absorbed from the GI tract and must be given parenterally.

Following IM administration of a single ceftriaxone dose of 0.5-1 g. in healthy adult, peak serum concentrations are attained 1.5-4 hr. after the dose (McEvoy, 1994).

In multiple-dose studies in healthy adults who received a ceftriaxone dosage of 0.5-2 g. given every 12 or 24 hr. by IM or IV infusion over 30 min. serum concentrations of the drug at steady state on the fourth day of therapy were 15-36% higher than serum concentrations attained with single dose of the drug (McEvoy, 1994).

Intravenous bolus administration of ceftriaxone 0.5 and 1.5 g. to healthy adult subjects resulted in mean peak plasma concentrations of 151 and 286 mg/L,respectively. Mean peak plasma ceftriaxone concentrations after intramuscular injection were around one-half those after intravenous administration of an equivalent dose, whereas AUC values (24 hr.) did not differ significantly indicating similar systemic bioavailability. After 2 hr. the mean plasma concentrations for these two routes were similar (Brogden and Ward,1988).

3.2 Distribution

In studies which examined the kinetics of both total and free ceftriaxone, the apparent volume of distribution of total (bound plus unbound) ceftriaxone during the terminal elimination phase increased with increasing dose, but volume of distribution of the free ceftriaxone (unbound) remained relatively constant. It was considered that the volume of distribution of total ceftriaxone at steady state corrected for total drug (Vd_{sstot}) did not change with increasing dose and the ratio of ceftriaxone in the body to total plasma ceftriaxone remains unchanged (Brogden and Ward, 1988).

Following IM or IV administration, ceftriaxone is widely distributed into body tissue and fluids including the gall bladder,lungs, bone, bile, prostate adenoma tissue,

uterine tissue, atrial appendage, sputum, tears, pleural, peritoneal, synovial, ascitic and blister fluids.

The volume of distribution of ceftriaxone is dose dependent and ranges from 5.8-13.5 L in healthy adults. The volume of distribution of the drug averages 8.5-9.4 L in healthy adults following a single 0.5 g. dose of the drug and 10-11.4 L following a single 2 g.dose (McEvoy, 1994).

Ceftriaxone generally diffuses into CSF following IM or IV administration, but only low concentrations are distributed into aqueous humor. The degree of protein binding of ceftriaxone is concentration dependent and decreases nonlinearly with increasing concentrations of the drug.

Ceftriaxone crosses the placenta and is distributed into amniotic fluid and cord blood, where peak concentrations of the drug occurred 4-8 hr. after the dose. Ceftriaxone is also distributed into milk in low concentration, peak concentration of the drug in milk occured 4-6 hr. after the dose and the AUC for milk was 3-4% of the AUC for serum (McEvoy, 1994).

3.3 Elimination

Ceftriaxone is eliminated unchanged by the kidney and the liver. The drug is excreted principally in urine by glomerular filtration and is also excreted in feces via bile.

Following IM or IV administration of a single dose of ceftriaxone in adult with normal renal and hepatic function, 33-67% of the dose is excreted in urine as unchanged drug and the remainder of the dose is excreted in feces as unchanged drug and microbiologically inactive metabolites (McEvoy,1994). The distribution Half-life ($t_{1/2\alpha}$) of ceftriaxone is 0.12-0.7 hr. and elimination half-life ($t_{1/2\beta}$) is 5.4-10.9 hr. Half-life is only slightly to moderately affected in patients with decreased renal function and relatively normal non-renal elimination but was increased in neonates and in patients over 75 years of age.

The percentage of a 0.5 g. intramuscular dose of ceftriaxone excreted unchanged in the urine during 48 hr. increased from around 35% following a single dose to 51% after multiple dose (Brogden and Ward, 1988).

Serum clearance of ceftriaxone is dose dependent and ranges from 9.7-25 ml/min in healthy adults.

4. Clinical Use and Efficacy

Because ceftriaxone has a long serum half-life and can be administered once daily. The drug may be useful in the management of infections caused by susceptible organisms that require prolonged therapy and can be administered to out-patient setting eg. osteomyelitis. Ceftriaxone has been used successfully for out patient treatment in adults and children and, in some case, the drug was self-administered (McEvoy, 1994).

4.1 Treatment of Established Infections

4.1.1 Urinary Tract Infections

A large number of patients with urinary tract infections, many of which were acute exacerbations of chronic infections or infections complicated by underlying urological abnormalities, have been treated with ceftriaxone. Response rates varied widely between studies, as did the type of infection, presence of predisposing factors, definition of a response and time to assessment. Hence, a "usual" response rate is difficult to establish even in patients with specific bacterial infections. Bacteriological findings were generally considered to be negative when $<10^5$ organisms or cfu/ml were present in the urine. Dosage ranged from 0.25 to 3 g/day IM or IV in 1 or 2 doses daily. The most common dosage was 1 g. 12 hourly for 5 to 10 days. (Richards et al., 1984)

4.1.2 Lower Respiratory Tract Infections

In studies conducted before 1984, the efficacy of ceftriaxone was generally determined using multiple daily dosage regimens. In more recent trials, ceftriaxone

usually been used at a dosage of 1-2 g. once daily. In a large multicenter trial, patients with pneumonia or chronic bronchitis were treated with ceftriaxone 1-2 g. IV and IM for 4-20 days. Therapeutic success was achieved in 96%, with eradication of bacterial pathogen occurring in 88% (Brogden and Ward, 1988).

4.1.3 Bacteraemia and Septicaemia

In the review of patients with bacteraemia, ceftriaxone 1-3 g. daily alone can be used successfully in the treatment of bacteraemia and septicaemia. The most common dosage was 1 g. 12 hourly for 5-10 days (Richards,1984). The review included only small numbers of patients, ie. over 100 patients, but have confirmed that ceftriaxone 1-2 g. once daily in adults or 50 to 75 mg/kg once daily or in two divided doses in neonates, infants and children, was effective in the treatment of bacteraemia/septicaemia caused by gram-negative or gram-positive aerobic bacteria (Brogden and Ward, 1988).

4.1.4 Sexually Transmitted Infections

4.1.4.1 Infections Due to Uncomplicated Gonorrhoea

The reports about ceftriaxone in the treatment of uncomplicated Neisseria gonorrhoeae infections have been confirmed in more trials in which a single IM dose of ceftriaxone 0.25 g. is recommended, particularly when infection is caused by penicillinase-producing or chromosomally mediated resistant strains. A single IM dose of ceftriaxone (0.25 g.) is recommended as the regimen of choice for the treatment of uncomplicated gonorrhoea in pregnant women. (McEvoy, 1994)

Gonorrhoea is frequently associated with coexisting Chlamydial and mycoplasmal infections. Ceftriaxone is ineffective for the treatment of infections caused by these organisms.

The US Centers for Disease Control (CDC) and the American Academy of Pediatrics (AAP) currently recommend the neonates born to mothers

with documented peripartum gonococcal infections receive prophylaxis with a single IM or IV dose (25-50 mg/kg not to exceed 125 mg) of ceftriaxone (McEvoy, 1994).

Gonococcal Ophthalmia Neonatorum

Although ceftriaxone given as a single 125 mg dose IM without subsequent topical antibacterial therapy suggest that it is an effective therapy for gonococcal ophthalmia neonatorum (Brogden and Ward,1988), there is no clinical or laboratory evidence of disseminated infection. The CDC and the AAP currently recommend 7 days of therapy with IV or IM ceftriaxone multiple-dose for the treatment of neonatal gonococcal ophthalmia (McEvoy,1994).

Acute Pelvic Inflammatory Disease and Epididymitis

Ceftriaxone is used for the treatment of gonococcal pelvic inflammatory disease (PID). The optimum regimen for the treatment of PID has not been identified. Because it may be difficult to identify the various causative organisms and because no single anti-infective agent is effective against all possible pathogens. The CDC and the AAP have suggested the use of ceftriaxone in combination with erythromycin or sulfisoxazole as possible regimens for acute PID in prepubertal children. The CDC also has suggested the use of ceftriaxone in combination with tetracyclines for the children older than 7 years of age.

A single IM dose of ceftriaxone 0.25 g. followed by oral tetracycline is recommended for the treatment of adult with acute sexually transmitted epididymitis caused by Neisseria gonorrhoea and/or Chlamydia trachomatis (McEvoy, 1994).

4.1.4.2 Non-Gonococcal Infections

Primary Syphilis and Chancroid

Clinical trial in Kenya indicated a high degree of efficacy with ceftriaxone in Haemophilus ducreyi chancroid. Patients who were treated with a single 1g. injection of ceftriaxone were apparently cured (Richards et al., 1984). The CDC and many

clinicians recommended that a single IM dose of ceftriaxone 0.25 g. was effective for the treatment of genital ulcers and as an alternative to erythromycin for the treatment of H. ducreyi chancroid (McEvoy,1994).

Patients exposed to primary, secondary or early latent syphilis were treated with a single 125 mg IM dose of ceftriaxone over a 3-month follow-up period, no clinical or serological evidence of infection was noted in 25 of 27 patients (93%) (Brogden and Ward, 1988).

4.1.5 Skin, Soft Tissue, Bone and Joint Infections

Ceftriaxone has been used successfully in bacteriologically confirmed infections of bone, and infected wounds of the skin and subcutaneous tissue such as cellulitis, abscess or necrotising ulcers. The usual dosage was 2 g/day IV or IM (as 1 or 2 doses) but a dosage as high as 2 g. every 6 hr. was administered to some patients with infections due to resistant organisms. The duration of therapy varied, with some bone infections being treated for longer than 2 months. Ceftriaxone has also been used for treatment in ear, nose and throat infections and in the treatment of patients with septic burns (Richards et al., 1984 ; Theron and Nel, 1983).

4.1.6 Serious Bacterial Infections

In the comparison of ceftriaxone 2 g. once daily and cefuroxime 1.5 g. plus gentamicin 80 mg. 3 times daily in 64 patients with serious bacterial infections, the overall cure rate was 94% in patients treated with ceftriaxone and 75% in those treated with the combination regimen. The efficacy of ceftriaxone 2 g. administered once daily was very similar to that of cefotaxime 2 g. 4 hourly. The most frequently reported infections in urinary tract infections, pneumonia and intra-abdominal infections were caused most often by Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae or Klebsiella species (Brogden and Ward, 1988).

4.1.7 Bacterial Meningitis

Ceftriaxone has been effective when used alone in neonates, children or adults for the treatment of meningitis because it enters the CSF with inflamed meninges, and low concentrations are bactericidal for most organisms which cause this condition, such as H. influenzae, N. meningitidis, S. pneumoniae, group B streptococci, E. coli and Klebsiella species (Richards et al., 1984 ; McEvoy, 1994).

Results of several controlled studies indicate that ceftriaxone used alone is as effective as combination therapy with ampicillin and chloramphenicol for the treatment of meningitis caused by susceptible organisms. Some clinicians suggest that ceftriaxone is a drug of choice for ampicillin- resistant H. influenzae meningitis in neonates and children (McEvoy, 1994) with 80-100 mg/kg IV or IM once daily administration (Brogden and Ward, 1988).

The treatment of adult meningitis has been less widely reported than paediatric meningitis, The dose for adult patients with meningitis was 45-100 mg/kg twice daily (Richards et al., 1984).

4.1.8 Infections in Cancer Patients

Ceftriaxone has recently been identified as a potentially useful agent in immunocompromised patients and several studies have reported results on its use. Ceftriaxone 2-3 g. in adults or 50 mg/kg in children once daily, either alone or in combination with other antibiotics, has been associated with a successful clinical outcome in 62.5-100% of febrile episodes in neutropenic cancer patients. It is usually continued for a few days after symptoms have abated (Brogden and Ward, 1988).

4.1.9 Infections Caused by Multi-resistant Bacteria and Pseudomonas Species

Although ceftriaxone has been used in the treatment of skin and skin structure infections caused by Ps. aeruginosa, treatment failure have been reported when

ceftriaxone was used alone in the treatment of urinary tract infections or respiratory tract infections caused by these organisms. Some of these failures occured because superinfection with resistant strains of Ps. aeruginosa occured during therapy with the drug. Many clinicians state the ceftriaxone should not be used alone in the treatment of any infections where Ps. aeruginosa may be present (McEvoy, 1994).

4.1.10 Miscellaneous Infections

Ceftriaxone 2 g. once daily for 4 weeks and 1 or 2 g. daily for 4 weeks (not stated whether once or twice daily) was effective in treating streptococcal or Haemophilus endocarditis (Brogden and Ward, 1988).

Ceftriaxone 3-4 g. in adults IV once daily for 7 days was as effective as a 14 day course of oral or IV chloramphenicol in the treatment of typhoid fever.

Lyme disease is a multisystem syndrome characterised by erythema chronicum migrans, aseptic meningitis, arthritis and a variety of neurological dysfunctions. The causative organism is a spirochaete, Borrelia burgdorferi, which unsuccessfully treated with antibiotics but in one study reported that ceftriaxone 4 g. daily for 14 days resulted in clinical improvement (Brogden and Ward, 1988 ; McEvoy, 1994).

4.2 Prophylaxis

4.2.1 Perioperative prophylaxis

Ceftriaxone has been effective when used perioperatively to reduce the incidence of infection in patients under 20 mg. contaminated surgery, including coronary artery bypass, open heart surgery, orthopedic surgery, or intra-abdominal surgery. The drug usually is administered 0.5-2 hr. prior to surgery to ensure adequate anti-infective tissue concentrations at the time of surgery (Richards et al., 1984 ; Brogden and Ward, 1988 ; McEvoy, 1994).

5. Adverse Effects

The majority of side effects of ceftriaxone were transient in nature, and seldom required discontinuation of therapy.

The most commonly adverse effects were gastrointestinal disturbances (2.04-3.45%). These usually constituted diarrhea, nausea and/or vomiting and abdominal pain. Hypersensitivity with dermatological reactions were seen in 0.84-2.08%. Local effects included phlebitis, and with intramuscular injection, pain were less than 1% (Richards et al., 1984 ; Brogden and Ward, 1988).

Table 1 Minimum inhibitory concentration (MIC) of ceftriaxone

Organism	MIC_{90} (μg/ml)
Acinetobacter	8-32
Actinomyces	0.5-16
Borrelia burgdorferi	0.1-1
Chlamydia	8-32
Clostridium	0.5-16
Enterobacteriaceae (ie. E. coli, Klebsiclla, P.vulgaris)	0.05-4
Haemophilus ducreyi	0.002-0.06
H. influenzae	0.003-0.03
Neisseria gonorrhoeae	
nonpenicillinase-producing	0.002-0.02
penicllinase-producing	0.001-0.15
N. meningitidis	0.001-0.025
Pseudomonas aeruginosa	64 or greater
Salmonella species	0.04-0.1
Shigella species	0.02-0.5
Staphylococcus aureus	3-8
S.epidermidis	16-50
Streptococci (group B)	0.06-0.78
S. preumoniae	0.15-0.25
S. viridans	0.8-4

6. Precautions and contraindications

Ceftriaxone is contraindicated in patients who are hypersensitive to any cephalosporins. Use of ceftriaxone may result in overgrowth of nonsusceptible organisms, especially candida, enterococci, etc. If superinfection or suprainfection occurs, appropriate therapy should be instituted.

Ceftriaxone should be used with caution in patients with colitis, it should be considered in the differential diagnosis of patients who develop diarrhea during ceftriaxone therapy. Since ceftriaxone can precipitate in the gall bladder, it should be used with caution in patients with pre-existing disease of the gall bladder, biliary tract, liver or pancreas, so that serial abdominal ultrasonography be performed during therapy.

Although dosage adjustments are not usually necessary when ceftriaxone is used in patients with renal impairment or hepatic impairment alone, because the drug is not removed by haemodialysis or peritoneal dialysis, serum concentration of the drug should be monitored in patients, with severe renal or both renal and hepatic impairment (MeEvoy, 1994).

7. Dosage and Administration

The recommended dosage schedule is 1 to 2 g. given once daily (or in equally divided doses twice a day) for a period of 4 to 14 days for adults and children over 12 years of age. The dosage, route and frequency of administration of ceftriaxone are determined by the severity of the infection, sensitivity of the causative organism and condition of the patient. In severe infections and in cases in which the pathogens are only moderately sensitive to ceftriaxone the daily dosage may be increased, but the daily dose should not exceed 4 g. The drug should usually be continued for a minimum of 48 to 72 hr. after fever abates or after evidence of bacterial eradication has been obtained (MeEvoy, 1994).

When given in doses exceeding 250 mg or to patients with little muscle mass, ceftriaxone for intramuscular injection should be dissolved in a 1% lidocaine solution and administered by deep intragluteal injection to minimise pain.

For the treatment of serious infections (other than meningitis) in infants and young children, the recommended daily dose is 50 to 75 mg/kg (not to exceed 2 g.), given in divided doses every 12 hr. In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 g.), given in divided doses every 12 hr., should be administered with or without a loading dose of 75 mg/kg.

In the treatment of uncomplicated gonorrhoea, a single IM dose of 250 mg. is recommended. For the prevention of surgical infection, a single dose of 1 g. administered 0.5 to 2 hr. before surgery is recommended (Brogden and Ward, 1988 ; McEvoy, 1994).