LITERATURE REVIEW

1. CEFOXITIN

Cefoxitin is developed by chemical modification of the cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. Its structure is similar to the cephalosporins, but is characterized by a 7 α-methoxy β-lactam which is responsible for the property of resistance to degradation by bacterial β-lactamases. Side chains, attached by chemical modification of the basic cephamycin nucleus, determine the specific antibacterial actions and other properties (Figure 1).

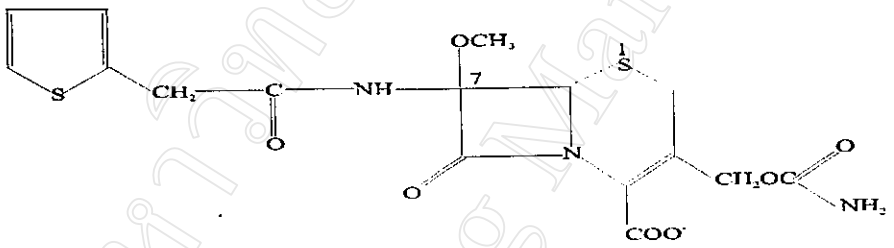

Figure 1 Structure of cefoxitin.

Antimicrobial activity

Cefoxitin has a broad spectrum of activity against both gram-positive and gram-negative bacteria. Its antimicrobial spectrum can be classified within the second generation cephalosporins. The drug is highly resistant to β-lactamase produced by gram-positive and gram-negative bacteria including *Escherichia, Klebsiella, Proteus mirabilis, Citrobacter, Legionella, Providencia,* some *Acinetobactor* and *Bacteroides* (Kass and Evans, 1979). It is more active than first- or other second-generation cephalosporins (except cefotetan and cefmetazole) against anaerobes, especially *B. fragilis* and some *Serratia.*

However, it is less active against gram-positive bacteria than the first-generation cephalosporins, and is not active against *Haemophilus influenzae,* enterococci and *Pseudomonas aeruginosa* (Wallick and Hendlin, 1974; Greaves et al., 1983). It is moderately active against *Staphylococcus aureus* and other gram-positive cocci, but *Streptococcus fecalis* is resistant as is *Listeria monocytogenes*. Anaerobic gram-positive cocci and gram-positive bacilli, including *Clostridia* and *Actinomyces*, are susceptible. *Enterobacter* are resistant. With respect to its antimicrobial activities, cefoxitin is particular useful for the treatment of mixed aerobic-anaerobic infections and certain anaerobic infections, such as peritonitis, diverticulitis, lung abscess, intra-abdominal infections and pelvic inflammatory disease (Sutterand Finegold, 1975; Bach et al., 1977; Chow and Bednorz, 1978). It is also effective against penicillinase-producing *Neisseria gonorrhea* (Greave et al., 1983).

Pharmacokinetics

Absorption

Cefoxitin is commercially available as sodium salt, which is not appreciably absorbed by oral administration and must be given parenterally (intramuscularly or intravenously). It is very rapidly absorbed from intramuscular sites. In healthy volunteers, a single intramuscular dose of 1000 mg cefoxitin produces mean peak plasma concentrations (C_{max}) of 22.0-31.7 ug/ml and time to reach peak plasma concentration (T_{max}) at 0.17-0.47 hr (Sonneville et al., 1977; Schrogie et al., 1978, 1979).

Distribution

Cefoxitin is 34 to 80 % bound to plasma protein, mainly to albumin (Gillett and Wise, 1978; Schrogie et al., 1978, 1979; Brogden et al., 1979; Mays et al.,

1990). Its volume of distribution ranges from 8.0 to 34.5 L in patients or volunteers with normal renal function (Kosmidis et al., 1973; Neu, 1978; Schrogie et al., 1978; Brogden et al., 1979; Vlasses et al., 1980; Reeves et al., 1981). The volume of distribution is increased in postpartum period (Gonik et al., 1984) and in elderly subjects (Garcia et al., 1980). Cefoxitin is widely distributed into body fluids and tissues including pelvic tissue (Bawdon et al., 1982; Greaves et al., 1983), pericardial fluid, heart tissues, muscle and adipose tissues (Nightingale et al., 1981). It passes into pleural and joint fluids (Barrueco et al., 1981), and is detectable in antibacterial concentrations in bile (Hanshrough and Clark, 1982). Nonetheless, penetration into normal cerebrospinal fluid is very poor (Chien et al., 1979). Cefoxitin readily crosses the placenta, and fetal serum concentrations may be equal to maternal serum concentrations (Dubois et al., 1981). Small amount of the drug is distributed into milk (Geddes et al., 1977; Dubois et al., 1981).

Elimination

Cefoxitin is almost entirely excreted via the kidney since less than 5% of the drug is desacetylated in the liver to inactive descarbamyl form. It is rapidly excreted by both glomerular filtration and tubular secretion (Brumfitt et al., 1974; Schrogie et al., 1978). Following an intramuscular dose of 1000 mg, approximately 90% of the drug is excreted in the first 12 hours and urinary concentrations greater than 3000 ug/ml are observed. Oral probenecid administered shortly before, or concomitant with cefoxitin usually slows tubular secretion and produces prolonged higher serum concentration (Vlasses et al., 1980). In normal volunteers and patients with normal renal function, average serum half-life of cefoxitin after an intravenous and an intramuscular dose is 0.6-1.5 hours (Sonneville et al., 1977;Andriole, 1978; Gillett and wise, 1978; Neu,

1978; Schrogie et al., 1978, 1979; Brogden et al, 1979; Vlasses et al., 1980; Kampf et al., 1981; Reeves et al., 1981; Gonik et al., 1984)

Dosage and administration

The usual adult dosage range is 1-2 g every 6-8 hours. Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of infection and the condition of the patients. Intramuscular preparation of cefoxitin could be constituted with 0.5% lidocaine hydrochloride solution (2 ml/g of cefoxitin) to minimize pain at site of injection. Intramuscular administration of this preparation results in similar concentration-time profile compared with cefoxitin constituted with sterile water for injection (Sonneville et al., 1977).

Adverse effects

Adverse effects of cefoxitin are similar to other members of the cephalosporins, but some effects frequently occur such as thrombophlebitis, skin rash, rising liver enzymes ,etc. (Winzum, 1978).

2. CEFTAZIDIME

Ceftazidime is a third generation cephalosporin which is highly resistant to wide range of β-lactamases. It has the following structure:

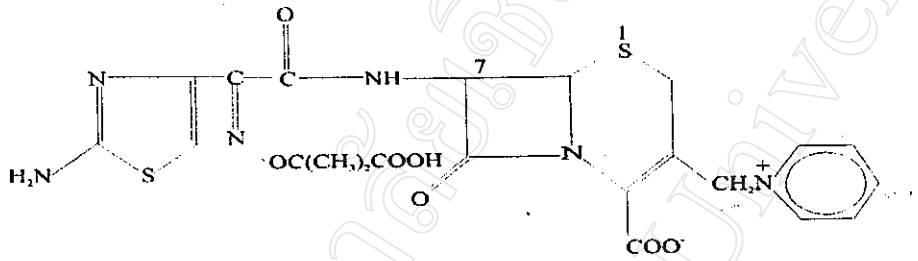

Figure 2 Structure of ceftazidime.

Antimicrobial activity

Ceftazidime is a broad spectrum antibiotic. It is active against most strains of gram-positive and gram-negative bacteria including ampicillin-resistant *H. influenzae* and *Enterobacteriaceae* (Callaghan et al., 1980; Neu and Labthavikul, 1982). Pathogenic bacteria associated with hospital-acquired infections and strains resistant to gentamicin and other aminoglycosides are generally susceptible to ceftazidime. The major distinguish features are its good activity against *P. aeruginosa* (Callaghan et al., 1980; Neu and Labthavikul, 1982) and its good penetration to the central nervous system that make it an agent of choice for the treatment of bacterial meningitis. Nonetheless, it is less active than other third-generation cephalosporins against gram-positive cocci such as *S. aureus* (Donowitz and Mandell, 1988) and has poor activity against *B. fragilis* (Hamilton-Miller and Brumfitt, 1981). Clinical uses include treatment of severe nosocomial infections; e.g., septicemia, peritonitis, pneumonia, meningitis and urinary tract

infection. The drug is also useful in the treatment of enterobacteria or *P. aeruginosa* infections in immunocompromised patients and/or neutropenic patients.

Pharmacokinetics

Absorption

Ceftazidime is commercially available as sterile powder containing a mixture of ceftazidime (as the pentahydrate) and sodium carbonate. It is not absorbed from the gastrointestinal tract therefore, must be given parenterally (Richards and Brogden,1985). Following an intramuscular administration of 1000 mg dose of ceftazidime in healthy adult volunteers, peak serum concentrations of the drug are attained approximately 1.12-1.73 hours after injection with average levels of 28.5-43.2 ug/ml (Harding et al., 1981; Tjandramaga et al., 1982; Sommers et al., 1983;).

Distribution

Ceftazidime is 5-22.8 % bound to plasma protein, mainly albumin (Kemmerich et al., 1983; Balant et al., 1985; Richards and Brogden, 1985; Lam et al., 1988; Mays et al., 1990; Paulfeuerborn et al., 1993). The degree of protein binding is independent of the serum concentration of the drug (Kemmerich et al., 1983; Richards and Brogden, 1985). The volume of distribution ranges from 15-20 L in healthy volunteers (Harding et al., 1981; Luthy et al.,1981; Sommers et al., 1983; Hedman et al., 1988; Paradis et al., 1992). The volume of distribution at steady state (V_{ss}) is 0.17-0.33 L/kg (Kemmerich et al., 1983; Leroy et al., 1984; Lam et al., 1988; Deeter et al., 1990; Paulfeuerborn et al., 1993) and the distribution half- life is 0.18-0.59 hour (Sommers et al., 1983; Kemmerich et al., 1983; Leroy et al., 1984; Heim-Duthoy et al.,1988; Deeter et al.,1990; Bressolle et al., 1992; Paulfeuerborn et al.,1993). Ceftazidime is widely distributed into body

tissues and fluid. Its concentrations in excess of the minimum inhibitory levels can be achieved in tissue such as bile/gallbladder (Loebis, 1985; Shiramatsu et al., 1988), skin and soft tissues (Loebis, 1985; Villavicencio et al., 1989), bone/synovial fluid (Villavicencio et al., 1989), skeletal muscle, myometrium, breast tissues, prostate gland and peritoneal fluid (Loebis, 1985) and sputum (Turner et al., 1984). Ceftazidime penetrates the intact blood-brain barrier poorly, however, therapeutic levels are achieved in the cerebrospinal fluid when the meninges are inflamed (Fong and Tomkins, 1984). Ceftazidime can cross the placenta and distributes to the amniotic fluid (Giamarellou et al., 1983). It is also excreted into breast milk (Blanco et al., 1983).

Elimination

Ceftazidime is not metabolized in the liver (Richards and Brogden,1985) and is principally excreted unchanged into the urine by glomerular filtration (Sommers et al., 1983; Hedman et al., 1988). Therefore, its elimination half-life is inversely correlated with the creatinine clearance. In adults with normal renal function, the elimination half-life is 1.45-4.42 hours (Harding et al., 1981; Luthy et al.,1981; Tjandramaga et al.,1982; Kemmerich et al., 1983; Sommers et al., 1983; Leroy et al., 1984; LeBel et al.,1985; Hedman et al., 1988; Heim-Duthoy et al.,1988; Lam et al., 1988; Deeter et al.,1990; Bressolle et al., 1992; Paradis et al., 1992; Paulfeuerborn et al.,1993). In patients with impaired renal function, its serum half-life is significantly prolonged and dosage adjustment is required. The serum half- life of ceftazidime is not changed in cystic fibrotic patients, however, is longer in premature/newborn infants and in elderly (Balant et al., 1985; Hedman et al., 1988; Bressolle et al., 1992).

Dosage and administration

The usual adult dosage is 1 g administered intravenously or intramuscularly every 8-12 hours. The dosage and route depend on the susceptibility of the causative organisms, the severity of infection, the renal function and the condition of the patients. Ceftazidime could be constituted with 0.5% or 1% lidocaine hydrochloride solution for intramuscular injection (3 ml/g of ceftazidime) to reduce pain at the injection site. This formulation does not alter the concentration-time profile in comparison with ceftazidime constituted with sterile water for injection (Chien et al., 1979).

Adverse effects

Adverse effects of ceftazidime are similar to other members of the cephalosporins. Generally it is well tolerated with no disulfiram-like effect. Nevertheless, some side effects have been observed including raised liver enzymes in liver function tests, eosinophilia, skin rash (Dominquez et al., 1989; Reinhardt et al., 1989; Trenholme et al., 1989), fever and diarrhea (Dominquez et al., 1989). Superinfection with resistant organisms, including *S. aureus,* enterococci *and Candida* or emergence of resistant strains of *P. aeruginosa* and *Enterobacteriacea* are usually associated with failure of therapy.