# INTRODUCTION

Ceftriaxone is one of the most commonly used antibiotics for treatment of serious bacterial infections (Cunha, 1985). Since chemically equivalent formulations from different manufacturers, refer as "innovator" and generic products differ widely in their methods of manufacturing, content of pharmacologically innert ingredients, dosage forms of the drug, and many other formulation variables, these factors can markedly influence the stability, amount and rate of drug release from the dosage form.

In recent years, controversy has arisen over the possible extent to which such generic products may or may not be therapeutically equivalent. Efforts are being made to design *in vitro* tests capable of predicting the *in vivo* performance of different products; however, *in vivo* studies of the bioavailability and pharmacokinetics, are currently the only reliable methods of ascertaining whether drugs are available from their formulations for absorption and production of therapeutic responses . Physicians are usually reluctant to use generic products that they consider not therapeutically equivalent. Generic products are generally less expensive and some of them are as effective as the innovator product, which may be considered more cost effective. Because of a lack of pharmacokinetic data of ceftriaxone in Thai subjects which is essential for appropriate dose adjustment, we designed this study to investigate the pharmacokinetic profiles of ceftriaxone including urinary excretion in healthy Thai volunteers, and to compare the stability and the relative bioavailability of two intramuscular dosage forms, 250 and 1,000 mg of a generic product, CEF-3 to the innovator preparation, ROCEPHIN.

# LITERATURE REVIEW

## Chemistry and stability

Ceftriaxone is a semisynthetic cephalosporin antibiotic, which is a highly polar compound (Granich and Krogstad, 1987). It is an aminothiazolyl cephalosporin containing an aminothiazolyl-acetyl side chain, with a methoxyimino group, at position 7 of the cephalosporin nucleus (Figure 1).

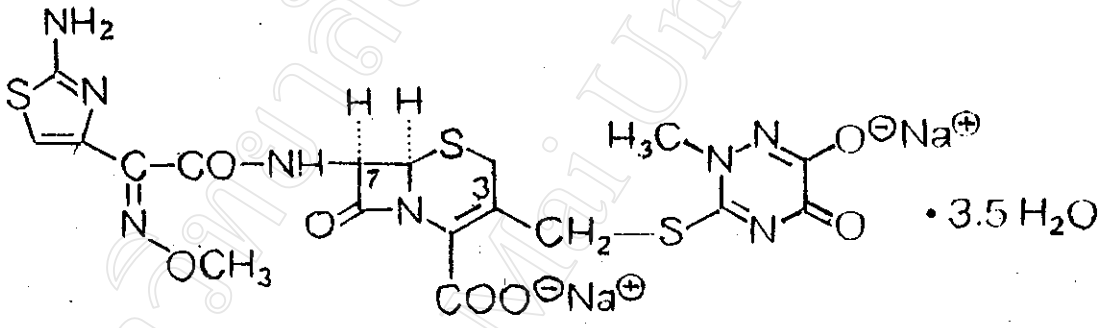

Fig. 1 Structure of ceftriaxone

The aminothiazolyl side chain enchances antibacterial activity, particularly against *Enterobacteriaceae* (Brogden and Ward, 1988) and the methoxyimino group imparts stability against hydrolysis by many beta-lactamase enzymes (Richards, 1984; Adam, 1990). Ceftriaxone also has an 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. Ceftriaxone sodium is readily soluble in water, having an aqueous solubility of 400 mg/mL at 25° C. The

drug has a solubility of 1 mg/mL in alcohol at 25° C. Ceftriaxone sodium has $pK_a$s of 3, 3.2, and 4.1 (Adam, 1990).

Mechanisms of action

Ceftriaxone, like other cephalosporins, is bactericidal in action; the antibacterial activity of the drug results from inhibition of mucopeptide synthesis in the bacterial cell wall. Although the exact mechanisms of action of ceftriaxone have not been fully elucidated, beta-lactam antibiotics bind to several enzymes in the bacterial cytoplasmic membrane (e.g.carboxy-peptidases, endopeptidases and transpeptidases) that are involved in cell wall synthesis and cell division (Jawetz, 1992). It has been hypothesized that beta-lactam antibiotics act as substrate analogs of acyl-D-alanyl-D-alanine the usual substrate for these enzymes. This interferes with cell wall synthesis and results in the formation of defective cell wall and osmotically unstable spheroplasts. Cell death following exposure to beta-lactam antibiotics usually results from lysis, which appears to be mediated by bacterial autolysins such as peptidoglycan hydrolases (Adam, 1990).

Pharmacokinetics

Most of the pharmacokinetic parameters of total ceftriaxone (both protein bound and unbound drug) except the elimination half-life ($t_{1/2}$) and unchanged fraction excreted in urine are dose-dependent and

increase nonlinearly with an increase in dosages (Stoeckel et al., 1981; Adam, 1990).

Absorption

Ceftriaxone is not appreciably absorbed from the gastrointestinal tract and must be given parenterally. Following an intramuscular administration of a single ceftriaxone dose of 500 mg in healthy adults and measuring serum concentrations of the drug over 24 hours, the maximal plasma concentration ($C_{max}$) is 41.9 ± 4.7 ug/mL, time to reach the maximal concentration ($T_{max}$) is 2.5 ± 0.8 hr, the area under concentration-time curve (AUC) is 577.0 ± 94.0 ug.hr/mL. and the absorption rate constant ($K_a$) is 0.94 ± 0.38 $hr^{-1}$ (Patel et al., 1982). The mean AUC values after an intramuscular administration of ceftriaxone are equivalent to those estimated after an intravenous administration of the equivalent dose, indicating complete bioavailability of intramuscular administered ceftriaxone (Patel et al., 1984; Scully et al.,1984 ).

Distribution

The degree of protein binding of ceftriaxone is concentration-dependent which decreases nonlinearly with increasing concentrations of the drug. It has been suggested that ceftriaxone may have more than one concentration- dependent protein binding site. The drug is 93-96% bound to plasma protein at a concentration less than 70 ug/mL, 84-87%

bound at concentration of 300 ug/mL, and 58% or less bound at a concentration of 600 ug/mL (Adam, 1990). Ceftriaxone binds mainly to albumin. Protein binding of ceftriaxone is lower in neonates and children than in adults because of lower plasma albumin concentrations in these age groups. The protein binding is also lower in patients with renal or hepatic impairment as the result of a decrease in plasma albumin concentrations or displacement from protein binding sites by bilirubin and other endogenous compounds that may accumulate. The volume of distribution ($V_d$) of ceftriaxone is dose-dependent and ranges from 5.8-13.5 L in healthy adults (Patel, 1984; Adam, 1990 ).

Although highly protein - bound, ceftriaxone shows good penetration into aqueous humour (Gobeaux et al., 1989), cerebrospinal fluid (Stecle et al., 1983), thoracic wall fat (Martin et al., 1992) and biliary tract (Steib et al., 1993).

Elimination

Plasma concentrations after an intravenous administration of ceftriaxone decline in a biphasic manner. In healthy adults, the distribution half-life of ceftriaxone is 0.4-1.3 hr and the elimination half-life ($t_{1/2}$ ) is 5.4-10.3 hr, the plasma clearance ($CL_p$) is 0.89 ± 0.1 L/hr and the constant value of elimination ($K_e$) is 0.1 ± 0.02 $hr^{-1}$, after a 500 mg dose of ceftriaxone intramuscular administration (Patel et al., 1982).

Ceftriaxone is not significantly metabolized and is excreted unchanged principally in urine by glomerular filtration (50-60%) and in feces via bile (40-50%). Renal clearance ($CL_r$) of ceftriaxone varies between 0.37-0.73 L/hr (Patel et al., 1984; Granich and Krogstad,

1987). Therefore, with increasing renal insufficiency, there is a potential for drug accumulation. Dose reductions are necessary in patients with both renal and hepatic dysfunction. In contrast, younger children probably eliminate ceftriaxone more rapidly, necessitating more frequent administration of this drug (Joos et al., 1984).

Therapeutic use of ceftriaxone

Ceftriaxone has a broad-spectrum activity against gram-positive and gram-negative pathogens. It is highly effective against *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Enterobacteriaceae*, and shows moderate activity against *Pseudomonas aeruginosa* (Beskid et al., 1981). It is remarkably resistant to various types of beta-lactamase (Stoeckel et al., 1981). This property, together with high intrinsic activity, prove to be of value in infections caused by organisms resistant to other cephalosporins. Ceftriaxone is used for the treatment of infections of the lower respiratory tract (Kuvabala et al., 1989), skin, bone and joint, intraabdominal, urinary tract, septicemia (Brogden and Ward, 1988), miningitis (Stecle et al.,1983 ) and gonorrhea (Judson, 1986 ; Adam, 1990 ), caused by susceptible organisms. Ceftriaxone has also been used for perioperative prophylaxis (Toth et al., 1991; Martin et al., 1992 ).

Minimum inhibitory concentration ($MIC_{90}$) of ceftriaxone for *Enterobacter cloacae, Staphylococcus aureus*, and *Pseudomonas aeruginosa* are 1-4, 4-8, and 4-64 ug/mL, respectively (Paradis et al., 1992) (Fig.2).

Ceftriaxone has a unique long serum $t_{1/2}$ of 8-12 hr which is much longer than other third generation cephalosporins (Bergan, 1987).

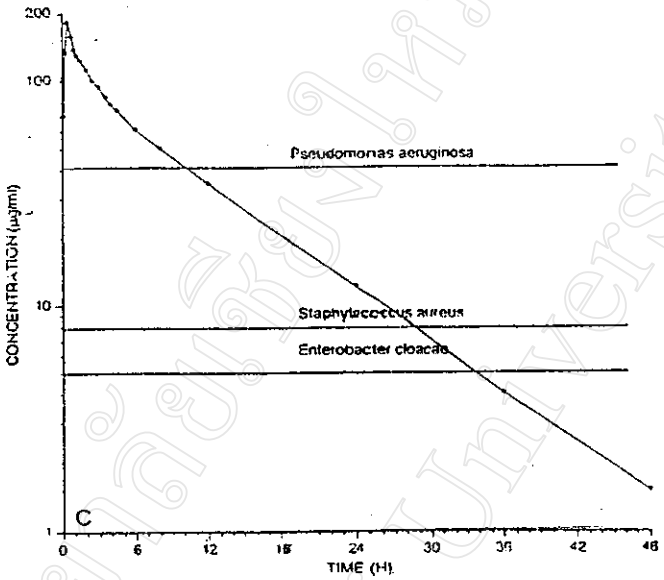


Figure 2. Plasma concentration - time curve of ceftriaxone after a single 1,000 mg intravenous dose of ceftriaxone and minimum inhibitory concentrations for certain organisms (Paradis et al., 1992).

This property permits 12-24 hr intravenous or intramuscular dosing intervals of the drug in most patients. For serious infections, ceftriaxone is usually given at the dose of 2 g intravenously every 12 hr (Cunha, 1985).

Adverse effects

Ceftriaxone is generally well tolerated, of the 2,640 patients who received ceftriaxone, 215 experienced clinical adverse effects judged to be possibly or probably related to treatment, with an overall incidence of 8.1%. The most frequent clinical adverse effects were related to the gastrointestinal tract, with a cumulative incidence of 3.45%. Other clinical adverse effects, in descending order of frequency, were hypersensitivity reactions (2.77%), local reactions at site of injection or infusion (1.86 %), central nervous system reactions (0.27%), candida overgrowth (0.23%), and various miscellaneous reactions totaling 0.42% (Morkovitz et al.,1984; Nilssion- Ehle; 1985; Zishka et al., 1990).

## OBJECTIVE

The objectives of this study are :

1. To compare the stability of ceftriaxone in the innovator ROCEPHIN and generic CEF-3 preparations, as a powder form and after reconstitution with the diluent.

2. To study the pharmacokinetics of the ROCEPHIN and CEF-3 preparations of ceftriaxone, when given intramuscularly.

3. To evaluate the relative bioavailability of the intramuscular CEF-3 preparation.