DISCUSSION

The stability of ceftriaxone in both ROCEPHIN and CEF-3 preparations appeared to be quite similar in our study. Dry powder form of ceftriaxone preparations were quite stable at all studied temperatures. An increase in the stability of the reconstituted form in 1% lidocaine solution was observed for both preparations when kept at low temperatures. The data were similar to the results observed from previous studies (Esteran 1990 and 1992). A change in the colour of the reconstituted ceftriaxone in 1% lidocaine solution was noted at 24 hr when kept at room temperature, but without any significant change in the amount of ceftriaxone in the solution. However, the amount of ceftriaxone in the reconstituted form rapidly and significantly declined afterward when kept at room temperature. An apparent increase in the amount of ceftriaxone in the reconstituted solution observed in this study after 9 days of storage at 0-4°C and -11°C was likely to be due to an evaporation of solvent from the solution.

The pharmacokinetics of intramuscular administration of ceftriaxone in healthy Thai volunteers appeared to be similar to the results observed in previous studies in caucasian subjects. (Patel et al., 1981; Holazo et al., 1982). Although statistical differences in the mean values of C_{max} ($p=0.01$) and V_d ($p=0.048$) were observed when a 250 mg dose of the two different preparations were given, the magnitude of differences were quite small and unlikely to have clinical significance. The plasma concentrations and the AUC_{0-24} of ceftriaxone increased less than dose-proportionally after 1,000 mg dosage. The increase in the mean C_{max} value after the 1,000 mg dose of ceftriaxone administration was 13.8 % less than the values predicted from the 250 mg

dose when linear pharmacokinetics was assumed and the ratio of AUC_{0-24} for the 1,000 and 250 mg dosages was found to be 3.1:1. These observations could be explained by the saturable plasma protein binding and the non-linear pharmacokinetic characteristics of total ceftriaxone (bound plus unbound), which was determined in this study, particularly when large dose was administered. Similar results have been reported previously (Stoeckel et al., 1981). The observation that the T_{max} was significantly longer for the 1000 mg dosage could be explained by the saturation or limitation of the rate of drug absorption from the site of intramuscular administration when a large dose was administered. This explaination was agreeable to the smaller K_a value observed for the 1,000 mg dosage comparing to the 250 mg dosage. The shorter $t_{1/2}$ and higher CL_p of ceftriaxone obtained from the plasma data which were observed when the 1,000 mg dose was given, could be explained by its distinctly non-linear concentration-dependent protein binding, resulting in a disproportional increase in free plasma concentrations (Richards et al., 1984). The mean plasma concentrations of ceftriaxone at 24 hr after either single dose of 250 mg or 1,000 mg intramuscular dosages in this study were found to exceed the minimum bactericidal concentration (MBC_{90}) of most *streptococcal species*, *Haemophilus influenzae*, and many of *Enterobacteriaceae* including beta-lactamase producing strains (Paradis et al, 1984). This finding indicated that 250 mg intramuscular dose of ceftriaxone at 24 hr interval might be adequate for treatment of septicemia, but higher dosage of ceftriaxone is necessary in the treatment of deep tissue infections and/or severe infections (Bradsher and Snow, 1984). However, a single 250 mg intramuscular dose of ceftriaxone is considered drug of choice for uncomplicated gonorrhea (Collier,

1984), particularly for homosexual men and when penicillinase-producing *Neisseria gonorrhoeae* (MIC_{90} = 0.025 ug/mL) and/or when chromosomally mediated resistance is prevalent (Judson, 1986).

The urinary excretion of ceftriaxone expressed as a percentage of the initial dose excreted unchanged in 24 hr and renal clearance were similar to those previously published (Patel et al., 1981) and were not different between the ROCEPHIN and CEF-3 preparations when the same dose was administered . The renal clearance of 1,000 mg dosage of ceftriaxone was estimated at intervals, a tendency toward lower renal clearance during the elimination phase was observed (Table 16 and Fig 8). These observations were dose and time dependent and could be explained by non-linear concentration-dependent protein binding as previously described (Patel et al., 1981). The rate of urinary excretion of ceftriaxone appeared to be parallel to the plasma concentrations; in other word, the amount of ceftriaxone excreted in the urine was directly proportional to the plasma concentrations. In addition, since the renal clearances of ceftriaxone were observed to be 0.37 ± 0.06 L/hr for the 250 mg dosage and 0.39 ± 0.10 L/hr for the 1,000 mg dosage, these observations might indicate that the renal elimination of ceftriaxone was governed mainly by glomerular filtration. This was confirmed from a probenecid-ceftriaxone interaction study which reveals that the pharmacokinetics of ceftriaxone are not altered by probenecid (Stoeckel, 1981; Stoeckel et al., 1981). The mean renal clearance (Cl_r) with reference to total ceftriaxone did not increase with dose because of a similar increase in the nonrenal clearance of ceftriaxone. We have compared the $t_{1/2}$ and K_e values of ceftriaxone estimated from the plasma concentration-time curves and from the urine excretion data for the 250 mg and 1,000 mg

dosages. There were no significant differences in the pharmacokinetic values obtained from either the plasma concentration-time curve or the urinary excretion data (Table 19). The urinary ceftriaxone concentrations even at 24 hr after a single 250 mg intramuscular dosage in the present study still exceeded the MIC_{90} and MBC_{90} of most of *E. coli*, *Morganella morganii*, *Klebsiella*, *Proteus* and *Providencia species*. The growth of most *Enterobacter species* is also inhibited (Paradis et al, 1992).

Since ceftriaxone is one of the most commonly used antibiotic for treatment of serious bacterial infections (Canha, 1985), the comparative pharmacokinetics and bioavailability study of a generic product would be necessary to ensure its bioequivalence to the innovator product, implying their "therapeutic equivalence". This information is necessary for a physician or practitioner considering a generic substitution of an innovator intramuscular preparation of ceftriaxone especially for patients with life-threatening or serious infections. Nonetheless, the results from this study have shown the bioequivalence of the two dosage forms (250 and 1,000 mg dosages) for intramuscular administration of this generic CEF-3 and the innovator ROCEPHIN products, since there were no differences in the mean AUC_{0-24} and other pharmacokinetic parameters tested when the two different products were given at the same dose. Thus, this generic CEF-3 product may be used interchangably with the innovator ROCEPHIN product particularly when the cost-effectiveness is concerned.

CONCLUSION

Ceftriaxone as dry powder form appeared to be quite stable at least up to 90 days at room temperature (26-30°C), 0-4°C and -11°C whereas its reconstituted form with 1% lidocaine solution appeared to decline over time when kept at room temperature. However the amount of ceftriaxone at 24 hr after reconstitution was not different from its initial amount. An intramuscular administrations of the generic CEF-3, both 250 and 1,000 mg preparations, yielded the same pharmacokinetic profiles as the innovator ROCEPHIN preparations.The mean relative bioavailability (F_{rel}) of this generic intramuscular preparation in comparison to the innovator product were 1.04 ± 0.22 and 1.00 ± 0.05 for the 250 and 1,000 mg dosages, respectively. Hence, both the 250 and 1,000 mg intramuscular dosage forms of these two products could be considered to be bioequivalent.