CHAPTER I

INTRODUCTION

Ceftriaxone is a third-generation cephalosporin with activity against a variety of aerobic and anaerobic gram-positive and gram-negative pathogens. Clinical studies have demonstrated its efficacy and safety (Nahata and Barson,1985). The drug is remarkably resistant to various types of β-lactamase. This property, together with high intrinsic activity, might prove to be of value in infections caused by organisms resistant to other cephalosporins (Stoeckel et al., 1981). Since ceftriaxone is not appreciably absorbed from the GI tract and must be given parenterally, there are two cormulars in ceftriaxone injections. One of these is for intravenous injection or infusion and the other is for intramuscular injection (McEvoy, 1994).

Ceftriaxone has a long serum half-life, about 8 hr. The drug is also 95% bound to serum protein (Findlay et al., 1982). Elimination half-life of ceftriaxone for 1 g. intravenous injection (IV) and intramuscular injection (IM) are 5.8±1.2 hr. and 5.4±0.8 hr., respectively (Meyers et al., 1983). The unusually long half-life gives ceftriaxone a potential advantage over other third-generation cephalosporins. The drug can be administered in lower dose and at longer intervals than currently available cephalosporins (Maslow et al., 1982).

The pharmacokinetics of ceftriaxone were investigated in healthy volunteers to whom 1 g. doses were administered IV and IM in crossover study. Pharmacokinetic parameters : area under the serum concentration-time curve (AUC), volume of distribution (Vd), elimination half-life ($t_{1/2}$) were compared (AUC = 830±284.0 and 903.5±588.9 μg.hr./ml ; Vd=0.2±0.03 and 0.19±0.15 L/kg. ; $t_{1/2}$=5.4±0.8 and 5.8±1.2 hr. for IV and IM, respectively) (Meyers et al., 1983). Most physicians assume that the IM route is reliable as the IV and that it results in equally complete bioavailability of the injected drug (Greenblatt and Koch-Weser, 1976).

Ceftriaxone intramuscular injections are available in Thailand through a variety of trade names from different manufacturers. However, the cost per unit of the products imported is 2-3 times higher than the locally manufactured brands. Most of the bioavailability

studies in healthy volunteers and/or patients have been carried out and reported in Europeans and Americans. In Thailand where ceftriaxone is also widely prescribed, the difference in race and biological behavior may contribute to the bioavailability difference of the drug, so that the bioequivalence of these ceftriaxone intramuscular injections should be evaluated.

This study is conducted to compare the bioequivalence of ceftriaxone intramuscular injections commercially available in Thailand and to investigate the pharmacokinetics of ceftriaxone after intramuscular injection in healthy volunteers.

Objectives

1. To compare the bioequivalence of ceftriaxone intramuscular injections commercially available in Thailand.
2. To investigate the pharmacokinetics of a single dose of ceftriaxone intramuscular injection in Thai male healthy volunteers.
3. To investigate the in vitro quality of ceftriaxone intramuscular injections according to the requirements of the official pharmacopoeia.

Significance of the Study

1. This study will provide the information about the bioavailability of ceftriaxone intramuscular injections commercially available in Thailand compared to the innovator's product which would be useful in the selection of an equally effective locally made product with lower price.

2. This study will provide the pharmacokinetics of ceftriaxone intramuscular injections in Thai male healthy volunteers which would be useful in clinical application including appropriate dosage regimens, dosage interval for the most effective administration.