CHAPTER I

INTRODUCTION

Background and Rationale

Gentamicin is an aminoglycoside antibiotic which is very water soluble, low serum protein binding range from 0 to 20% and about 90% is excreted unchanged in urine. Gentamicin is widely used to treat patients with serious gram-negative bacteria infections. However, since aminoglycosides have narrow therapeutic range (nephrotoxicity and ototoxicity may occur from overdose while underdose will result in non-effective treatment and development of bacterial resistance), various studies have examined the effects of serum concentrations on toxicity. Peak levels of greater than 12 µg/ml and trough levels of greater than 2 µg/ml have been correlated with a high incidience of nephrotoxicity. Trough levels of greater than 2 µg/ml are probably associated with an increased risk of ototoxicity (Zaske,1980b).In additions, there is striking interpatient and intrapatient variation in pharmacokinetics of the aminoglycosides for patients with normal and abnormal renal function. This results the differences in peak concentration and drug clearance. The variation in serum aminoglycoside concentrations is dependent on renal function and the volume of distribution, both of which are partially affected by patient factors including age, weight, gender, fever, and

concurrent disease states (Rodvold, Zokufa and Rotschafer, 1988). Therefore ,therapeutic drug level monitoring for an individual patient is necessary for desired serum level in order to improve therapeutic response or reduce toxicity.

Individualized pharmacokinetic approaches was attempted to measure the distribution volume and the elimination rate constant on a patient-by-patient basis. Using these pharmacokinetic values generated from measured serum concentration-time data, the clinical pharmacist can determine the appropriate dose and dosage interval needed for an individual patient in order to achieve desired peak and trough concentrations. One of the individualized methods,Sawchuk-Zaske, has been used frequently for providing aminoglycoside pharmacokinetic dosing services. This method has been tested widely in burn patients , geriatric patients , surgical patients , obstetric patients and other patients with gram-negative infection. The Sawchuk-Zaske method has been shown to be more accurate than empiric dosing or nomograms for predicting the aminoglycoside dose necessary to acheive specific serum concentrations (Bloome et al,1988; Franson et al,1988 ; Rodvold, Zokufa and Rotschafer, 1988).

The time at which blood samples are drawn is essential for serum aminoglycoside concentration interpretation.The proper timing of blood samples must be determined for true trough or peak serum concentration, otherwise adjusting dosage regimen and interpreting serum drug concentration data will be inaccurate.

In recent years, many countries especially the United States, pharmacokinetics has been applied for the calculation of appropriate drug dosage for an individual patient in several hospitals. In Thailand, even though few studies about aminoglycosides have been reported, none of them was about the application of pharmacokinetics for therapeutic drug level monitoring.

This study is therefore set up in order to apply pharmacokinetic theories to calculate the appropriate drug dosage regimen for Thai patients and also to initiate the possible method for therapeutic aminoglycoside drug level monitoring in Thai patients.

Objective

1. To apply pharmacokinetic theories for estimation of the appropriate gentamicin dosage regimen for individual Thai patient.

2. To compare percentage of patients whose serum level concentrations were within therapeutic range before and after the dosage regimen was adjusted by pharmacokinetic approach.

3. To compare the pharmacokinetic predicted serum concentrations with the measured values.

4. To evaluate whether the equations used for calculation in the present study were appropriate for Thai patients.

5. To create appropriate basic pharmacokinetic parameters data for Thai patients to put in the computer program for future use of gentamicin dosage regimen

adjustment in Thai patients.

6. To initiate the possible method for therapeutic drug level monitoring in Thai hospitals using gentamicin as the model drug.

The Significance of the Study

1. This study will provide the answer whether the pharmacokinetic calculated dosage regimen will result in higher percentage of patients with therapeutic range of serum gentamicin concentrations as compared to the traditional physician used dosage regimen.

2. This study will provide the answer that whether the pharmacokinetic parameters calculated from the patients'serum creatinine and some of their general characteristics were comparable to those values obtained from a few measured serum gentamicin concentration.

3. This study should be an initiation of the possible method for therapeutic aminoglycoside drug level monitoring in Thai patients.

4. This study should provide some pharmacokinetic parameter basis data of Thai patients which may be used to create equation and/or computer program for proper estimation of the gentamicin dosage regimen in Thai patients in the future.