CHAPTER I

INTRODUCTION

Background and Rationale

Theophylline has been one of the most frequently reviewed agents in the drug literature. Since the early 1970S, the pharmacodynamics and pharmacokinetics of this drug have been more clearly defined, resulting in safer and more efficacious use, Although this drug has been used as a respiratory stimulant for Cheyne - Stokes respirations, in acute pulmonary edema, and in the treatment of apnea in premature newborns, its major use has been for the prophylactic treatment of chronic asthma (Iafrate and Blake, 1992). Theophylline therapy is of significant value in the management of chronic asthma has been recommended for use as a first - line agent in the treatment of chronic asthma (Edwards, Zarowitz and Slaughter, 1992). In addition, theophylline is used for treatment of reversible bronchospasm that may occur in assosiation with chronic bronchitis or emphysema (McEvoy, Litvak and Welsh, 1993). Theophylline preparations are extensively utilized bronchodilators in the treatment of Chronic Obstructive Airways Disease (Gotz, 1993).

Application of new knowledge related to the pharmacodynamic and pharmacokinetic characteristics of theophylline and the availability of rapid specific serum assays, have improved both the efficacy and safety of this drug. In addition, reliably - absorbed, slow - release formulations have been developed that provide a highly effective and convenient means of maintaning around - the - clock stablization of the hyper - reactive airways that characterize chronic asthma (Hendeles, Massanari and Weinberger, 1986). Theophylline is useful in the treatment of nocturnal asthma. The slow - release preparations provide therapeutic concentrations overnight and are more effective for this purpose than slow - release beta - adrenergic agonists (Barnes, 1992).

Theophylline is a model drug for demonstrating the value of therapeutic drug monitoring in clinical medicine because of preeminence of theophylline is based upon the follwing (Ellis and Hendeles, 1986; Gibaldli, 1991; Goldsmith, 1992; Hendeles, Weinberger and Johnson, 1987) :

1. Theophylline has a narrow therapeutic index.
2. There is large interpatient variability in rate of theophylline elimination.

3. Serum concentration may be affected by many factors that affect liver microsomal enzyme function and alter elimination kinetics.

4. The good correlation between plasma theophylline levels and both efficacy and toxicity.

5. The large variability in the dosage requirements of theophylline .

This study was designed to investigate serum drug levels and clinical responses of theophylline therapy in Thai patients , to apply pharmacokinetic theories to adjust for the appropriate dosage regimen in individual Thai patients by assessment from clinical responses and theophylline serum level, and to compare the calculated drug levels from literature (predicted values) with the measured drug levels in blood (measured values).

Objectives

1. To assess whether the dosage regimen of theophylline for treatment of respiratory disorder in Thai patients is in therapeutic range and assess incidence of adverse reactions and/ or no beneficial effect of theophylline therapy in Thai patients.

2. To assess the correlation between theophylline serum concentrations and clinical responses to theophylline therapy for beneficial effects and adverse reactions of theophylline in Thai patients treated with theophylline.

3. To apply pharmacokinetic theories to adjust for the appropriate dosage regimen in individual Thai patients when theophylline serum concentrations are inappropriate by assessment from adverse reaction occuring and /or no beneficial effect of theophylline in individual Thai patients.

4. To compare the theophylline serum concentrations obtained from the patients (measured values) with the calculated concentrations from pharmacokinetic parameters and equations from literature (predicted values).

5. To initiate the possible method for theophylline therapeutic level monitoring for Thai patients.

The Significance of the Study

1. This study will enable to justify whether the dosage regimen which is currently used by traditional physician prescribing practice will provide appropriate theophylline serum level.

2. This study will provide the information about the assessment of correlation between theophylline serum concentrations and clinical response to theophylline therapy (e.g., beneficial effects and adverse reactions of theophylline) in Thai patients treated with theophylline given according to the physician traditional dosage regimen.

3. This study will provide the information about clinical response improvement to theophylline therapy after the appropriate theophylline dosage regimen adjustment for individual Thai patients.

4. This study will enable to determine whether the pharmacokinetic parameters and equations that are widly used in foreign countries can be used to predict theophylline levels accurrately. If so, this method shall be recommended for calculating dosage regimens of theophylline for Thai patients.

5. This study will provide some pharmacokinetic parameters of theophylline in Thai patients which may be used as the data for calculating the appropriate dosage regimen for each individual patient either manually or when computer program is applied.

6. This study should provide the information about an initiation of the possible method for theophylline therapeutic level monitoring and could be able to apply to another drugs therapeutic level monitoring for Thai patients.