

# CHAPTER 1

## INTRODUCTION

### Introduction

Theophylline, a xanthine derivative, has been widely used for chronic asthma and other lung disease such as emphysema and chronic bronchitis (Labeling Guidance, 1995). In recent years, however, the use of theophylline in industrialized countries has declined. There are a number of reasons. Among them are as follow: 1) There have been other more appropriate medications available especially for the cases of asthma associated with pathogenic inflammation, for examples, inhaled steroids and, more recently, inhaled  $\beta_2$  agonists. 2) The different guidelines to third-line therapy for chronic asthma is indicated only as an additional bronchodilator agent for patients who are not controlled by dose-optimized inhaled steroids and adrenoceptor agonists (McElnay., et al. 1982; Brown and Lee, 1992; Otero., et al. 1996). 3) Theophylline has a narrow therapeutic index. Adverse effects are usually related to serum concentrations. 4) Clearance is highly variable and this has led to the recommendation that serum concentrations should be monitored to adjust theophylline dosage (Otero., et al. 1996).

There were many reports that studied theophylline dosage by utilizing pharmacokinetic population. Thus, it may be useful in enhancing the effectiveness of anti-asthmatic therapy while keeping the direct cost of the monitoring to a minimum. In most instances, it seems worth measuring serum theophylline concentrations when other conditions known to alter theophylline metabolism exist, such as smoking or disease factors (Otero., et al. 1996). The individual methods of Chiou, Koup and Vozeh found that all methods continue to be rapid

and accurate. The most recent cost-effectiveness data has shown that pharmacokinetic dosing program resulted in fewer toxic serum concentrations (18.9% *V.S.* 37.8%), and shorter mean duration of hospital stay (6.3 day *V.S.* 8.7 day) than among control patients receiving dosages prescribed by physicians (Erdman, et al. 1991). Previously, theophylline therapeutic level monitoring was studied in 61 Thai patients in Ratchaburi hospital. Patients initially treated with dosage regimen determined by physicians. It was found that 45.76% had theophylline serum concentrations in subtherapeutic range and 40.68% had their theophylline serum concentrations within therapeutic range. Beneficial effect of theophylline could not observe in 10.17% of patients. While incidence of theophylline adverse reactions were showed in 25.42% of the patients. Adverse reactions of theophylline which occurred most often in the patients were pulse rate  $\geq 100$  bpm, palpitation, and gastrointestinal effect (Jarunee, 1995). Jeene., et al found that about 10 percent were definitely toxic, for the most of these consists of unpleasant gastrointestinal side effects. All such patients had routine serum theophylline level over 13 mcg/ml. Non of the patient with level under 13 mcg/ml that showed sign of toxicity, whereas it was very common for patient with level over 20 mcg/ml.

In Maharaj Nakhonsrithammaraj hospital, in the preliminary study in which 72 patients were therapeutically monitored illustrated that 51.31%, 22.36%, and 26.31% of the subjects had serum theophylline concentrations in subtherapeutic, therapeutic, and toxic levels, respectively. Theophylline has narrow therapeutic range within 10-15 mcg/ml (USFDA, 1996). Therapeutic drug monitoring of theophylline is therefore necessary but the cost of the monitoring is somewhat expensive making the activity unlikely possible. The application of theophylline dosage utilizing the population pharmacokinetic parameters with medical diagnosis may be useful to increase efficacy, decrease toxicity, decrease work load of pharmacists and decrease cost of treatment. The aim of this study is to validate

Theophylline dosage program by comparing the different of theophylline level between dose from Theophylline dosage program and the actual level. Now in Maharaj Nakhonsrithammaraj hospital there are a lot of patients who have been using theophylline, but have not yet improved, and sometime, got toxicity because of the condition of patients or drug interaction. So, calculated theophylline dose with the use of factors affecting drug clearance may be increase the efficacy and decrease toxicity of theophylline including decrease in the cost of treatment for some patients who are not necessary for theophylline monitoring.

### **Objective of the Study**

This study was conducted to evaluate the precision of the patient's individual dose determined by Theophylline dosage program.