



## CHAPTER I

### INTRODUCTION

#### Background and Rationale

Theophylline is an important bronchodilator commonly used to treat acute and chronic asthma or bronchitis (1). Its therapeutic and toxic effects have been demonstrated to relate directly to serum concentrations (2-6). The drug has a narrow therapeutic serum concentration range of 10 to 20 mcg/ml (1,7-9). Lower serum concentrations are commonly not as efficacious, whereas toxicity has been commonly associated with serum concentrations greater than 20 mcg/ml. Adverse effects associated with serum concentrations above 20 mcg/ml are persistent, including nausea, vomiting, headache, diarrhea, irritability, insomnia (4,7), and at higher levels, seizures, brain damage, cardiac arrhythmias, and death (5,6). Furthermore, to achieve the proposed therapeutic concentration range of 10 to 20 mcg/ml, the final dosage adjustments ranged from 320 mg to 2,500 mg of theophylline per day (7). This large variation in dosage requirement is a reflection of the wide range of each patient's ability to clear the drug from the body. In another word, the total body clearance of theophylline

varies among individuals. It has been shown that many factors can affect the total body clearance of theophylline and therefore alter dose recommendations for individual patients. Some of these factors include age, smoking status, liver disease, and congestive heart failure (10).

Many previous studies reported that the total body clearance of theophylline in children was significantly higher than in adults (11-14), indicating that children could eliminate the drug faster than adults. It has been known that higher doses of theophylline are required to produce a similar steady-state serum concentration in children as apposed to adults (13,14). In the same way, smokers also eliminated theophylline more rapidly than nonsmokers as reflected by the higher elimination rate and clearance (15-19). The effect of cigarette smoking on theophylline clearance may be an important consideration in the clinical use of this drug. In contrast, theophylline clearance was markedly reduced in patients with congestive heart failure (20,21) or cirrhotics (22) compared to normal subjects, corresponding to longer elimination half-life. Thus, theophylline dose for these patients must be lower than the usual dose.

Conflicting reports have been published on the influence of sex on theophylline clearance (6,10,17,23, 24). Some investigators found no effect of sex on theophylline clearance either in children or adults (17,23), whereas the others showed a significantly higher

theophylline clearance in young males than in young females (10,24). However, a study suggested that male patients should receive lower dose of theophylline than female patients (6). Thus, the effect of sex on this drug should be clarified by further investigations.

The above reasons led to a variation in dosage requirement for individual patients. Therefore, pharmacokinetics was used to estimate the appropriate dose for each patient. In many countries, several studies were performed to define theophylline pharmacokinetics in the normal subjects compared to the subjects with various factors affecting theophylline kinetics in order to obtain the pharmacokinetic parameters for calculating the dosage regimen among individual patients.

However, only a few investigators have studied theophylline pharmacokinetics in Thais, and none of them have studied on the factors which may affect theophylline kinetics. Recently, two studies have shown that the elimination half-life ( $t_{1/2}$ ) of theophylline in Thai asthmatic children (8 to 13 years of age) was longer than that of Caucasians (25,26). Therefore, race may be a factor that has an influence on theophylline kinetics. A study on therapeutic drug monitoring in Ramathibodi Hospital (27) showed that the plasma theophylline levels of only about 34.2% of Thai patients were within the therapeutic level of 10 to 20 mcg/ml, whereas those of 45.2% reached toxic level ( $> 20$  mcg/ml). These may be resulted from using inappropriate dosage regimen as

studied in other countries. Therefore, this research was designed to study pharmacokinetics of theophylline in Thais, to investigate the effects of smoking status, sex and age on theophylline kinetics and to determine the pharmacokinetic parameters which would be useful for individualizing dosage regimen for Thai patients.

### Objectives

1. To study the pharmacokinetics of theophylline after oral administration of theophylline syrup in various groups of Thai healthy volunteers, i.e., smoking and nonsmoking males, nonsmoking females, and children.

2. To compare the pharmacokinetic parameters of theophylline in Thai healthy volunteers, between smoking and nonsmoking males, nonsmoking males and females, and adults and children.

### The Significance of the Study

1. This study will provide the pharmacokinetics of oral theophylline in Thais. The information obtained will be compared with previous studies conducted in other countries, in order to investigate the effect of race on theophylline kinetics.

2. The pharmacokinetic parameters of theophylline obtained from this study would be useful in determining dosage requirements for Thai patients, in order to achieve

the optimal benefit and safety for clinical use of this drug.

3. The information obtained would confirm whether smoking, sex or age can affect theophylline kinetics in Thais.

4. This research will be a study model for other drugs, which have a wide variability in pharmacokinetics among individual patients.