CHAPTER I

INTRODUCTION

For decades theophylline has been recognized as a potent bronchodilator for the relief of acute asthmatic symptoms, as a respiratory stimulant for Cheyne-Stokes respirations, and as an adjunct in the treatment of acute pulmonary edema. More recently it has been used to prevent episodes of idiopathic apnea or bradycardia in premature newborns. Its most important current use, however, is as a major prophylactic agent for controlling the symptoms of chronic asthma. (Hendeles, Massanari and Weinberger, 1986)

Despite the use of theophylline since the 1930's, a definitive mechanism of action of the drug has been questioned.

Later, it is found that there is a significant relationship between serum theophylline concentration (STC) and efficacy and toxicity. 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. (Jacobs, Senior, Kessler, 1976)

However, theophylline is so rapidly absorbed, thus liquid formulations and conventional plain tablets that undergo rapid dissolution are frequently associated with excessive fluctuations in serum concentrations even when intervals between doses are as short as six hours. (Upton et al., 1980) Formulations that decrease the rate of absorption potentially result in more stable serum concentrations. (Hendeles, Iafrate, and Weinberger, 1984)

Sustained-release theophylline products are formulated in various ways that decrease the rate of disintegration and dissolution of the drug. The resulting products, however, may differ to clinically

important degrees in completeness, rate, and consistency of absorption and can be marketed without approval for bioequivalence from the Food and Drug Administration (FDA) (as many have). Furthermore, current criteria for FDA approval do not ensure the general applicability of advertising claims for twice-daily or once-daily dosage administration in Thais. Consequently, data used to support claims for product performance must be examined critically.

At present, there are four different brands of theophylline sustained-release tablets commercially available in the market. One is a well-known innovator's product which have complete bioavailability and can be used as reference for bioavailability study.

Although theophylline sustained-release tablet has been used for many years, no completely comparative bioavailability data and phamacokinetic characteristics of these products available in Thais. Therefore, an extensive study was conducted to provide the bioavailability of different commercially theophylline sustained-release tablets and to assess the pharmacokinetics of theophylline sustained-release after multiple-dose oral administration in Thai healthy volunteers.

Objectives

1. To assess that theophylline sustained-release tablets made by many manufactures have equal quality both in vitro and in vivo.

2. To investigate the pharmacokinetics of theophylline sustained-release tablets after multiple-dose oral administration in Thai healthy volunteers.

3. To determine statistically the relationship between the in vivo (dissolution content and rate) and the in vivo data (C_{max}, T_{max}, AUC, % fluctuation, etc.).

Significance of the study

1. To be able to justify whether theophylline sustained-release tablets commercially available in Thailand bioequivalent which medical staffs or regardings have data to select the most economial products or to substitute between the products with the same bioavailability.

2. This study will provide the information on the pharmacokinetics of theophylline sustained-release in Thai healthy volunteers.