INTRODUCTION

Theophylline is a bronchodilator commonly used in the treatment of asthma and chronic obstructive pulmonary diseases (COPD). The drug has been used as a major prophylactic agent for nocturnal asthma and exercise induced-asthma as well as an agent to reduce the need for oral steroid medication[1-5]. Its therapeutic effects are not only due to bronchodilatation but also include immunomodulatory effects and antiinflammatory activities[4-7]. Theophylline is particularly effective in controlling late-phase asthmatic reactions and the development of airway hyperresponsiveness in asthma patients[5]. Moreover, its ability to improve mucociliary clearance, ventilatory drive, and contractility of the diaphragm provide therapeutic benefit to COPD patients[8]. Furthermore, it may enhance diuresis, improve cardiac output, reduce systemic and pulmonary vascular resistance and decrease microvascular permeability[7].

Despite these beneficial effects, the use of theophylline is limited because of its narrow therapeutic window and the requirement of monitoring of drug levels. Acceptable therapeutic plasma levels of theophylline ranges between 5-15 μg/ml[9]; since some patients may have significant improvement in respiratory functions at lower plasma concentrations (5 μg/ml)[10]. Higher theophylline levels (>20 μg /ml) are potentially associated with drug toxicity[7]. The symptoms of theophylline toxicity include nausea, vomiting, anxiety, tremor, headache, and palpitation. Life-threatening arrhythmias, seizures as well as serious metabolic abnormalities have been reported with acute theophylline intoxication[7]. To minimize the risk of developing side effects, therapy should be started with a low dosage, thereafter, increasing the dosage slowly to maintain the lowest plasma concentration that produces therapeutic effects. Dosages required to achieve therapeutic levels of theophylline vary widely from patient to patient due to its differences in hepatic

metabolism. The dosages may range from less than 10 mg/kg/day to 36 mg/kg/day or higher for patients with faster rates of elimination[11]. In these patients, the elimination half-life is usually short, therefore traditional theophylline preparations with rapid absorption will result in large fluctuation in serum theophylline concentrations. Since fluctuation in plasma theophylline concentrations may alter its ability to stabilize the airway reactivity and may result in drug toxicity, sustained-release theophylline preparations (SRT) have therefore been developed. These preparations will provide slower and continuous release of theophylline in the gastrointestinal tract.

Most of the SRT preparations are designed to release theophylline at a constant zero-order rate over the dosing interval. The advantage is the ability to use less frequent dosing to maintain its plasma concentrations within therapeutic range with less fluctuation in its steady-state concentration. Nevertheless, the ability of the SRT to maintain theophylline concentration within its therapeutic range is not only due to a function of the rate of release of theophylline from the product but also depends on theophylline clearance rate of the patient. Therefore, SRT formulations are particularly beneficial for patients with theophylline half-life of less than six hours. Furthermore, for around the clock theophylline therapy in asthma patient, SRT preparations are recommended since fewer daily dosing enhances patient compliance and results in better asthma control. In addition, they permit improved maintenance of therapeutic levels throughout the day and night.

Currently a large number of SRT preparations have been marketed. Although oral theophylline tablets are highly bioavailable, great variations exist in the percentage of absorption among the SRT products, since they vary greatly in their intestinal release and rate of absorption[12]. For the products that have longer duration of absorption, administration every 8 to 12 hours is usually acceptable. Generally, the use of these products as twice-daily dosing schedule results in less peak-to-trough variations than once-daily dosing. Furthermore, patients with rapid elimination half-

lives or those requiring serum concentrations above 10 μg/ml may have greater therapeutic effect with twice a day dosing[13]. Nonetheless, dosage forms that can be administered once daily are available. These products are indicated for patients showing normal or low theophylline clearance and for controlling nocturnal or morning asthma symptoms. However, the disadvantage of the once-daily products is the possibility of incomplete bioavailability, especially for the ultraslow formulation[14-17] since their duration of absorption may exceed the gastrointestinal transit time thus results in an incomplete absorption. Food also has a variable effect on the rate and extent of SRT absorption. The extent of theophylline absorption when administered with food may be greater than after fasting. This phenomenon is known as "dose-dumping" which is a matter of concern for once-daily SRT preparations[18-21]. Another factor affected SRT absorption is diurnal variation or day-night differences in drug absorption. Higher peak concentrations and faster time to peak concentration are seen with morning dosing as opposed to evening dosing[22].

Kanthawatana et al. had conducted a single-dose pharmacokinetic study of three SRT oral preparations available in Thailand[23]. The pharmacokinetics and bioavailability of the three SRT oral preparations; Theo-Dur®, Theo-24® and Xanthium® were investigated in 12 healthy Thai subjects. Theo-Dur® is an extended-release tablet available for 12-hour dosing interval, while Theo-24 and Xanthium® are ultraslow sustained-release formulations, which allow 24-hour dosing interval. The latter preparation is a bead-filled capsule that get their sustained-release characteristics by the use of varying thickness of coating, with the thinner coating dissolving at a faster rate than the beads with thicker coating. In that study, the relative extent of absorption (F_{rel}) of Theo-24 and Xanthium® were 97% and 78% of Theo-Dur® respectively. The reason for a lower bioavailability of Xanthium® may be due to the limitation of bead coating in delaying the rate and extent of absorption

comparing to Theo-Dur®, a faster release formulation. Nevertheless, that study may underestimate the extent of absorption of the ultraslow-release preparation since it was conducted as a 36-hour single-dose study and theophylline absorption might take place beyond the end of the study period. Therefore, multiple-dose, steady-state pharmacokinetic study is required to determine the absorption characteristic of once-daily SRT preparations.

Recently, Theo-24® has been withdrawn from the Thai market and Uni-Dur®, a SRT tablet formulation intended for once-daily administration is introduced to our country. Uni-Dur® has been approved by the US-FDA and legally marketed in 1995. When administered once daily in the morning, the drug exhibits better extended-release characteristics compared with a reference extended-release twice-daily product. Moreover, based on an adverse event monitoring, there is no evidence of "dose-dumping" since theophylline absorption from Uni-Dur® is not affected by food[24]. Since the pharmacokinetic characteristics and their oral bioavailability at steady state of the SRT products have never been investigated in Thai subjects, this study aims to compare the steady-state pharmacokinetic profiles of SRT available in Thailand. Only male subjects will be enrolled because changes in theophylline clearance occur during the menstrual cycle in women[25]. In addition, prescreening for theophylline clearance will be determined to exclude subjects with slow theophylline clearance who may develop saturation in drug elimination at steady-state.

The results of the study can be used as a guideline in selecting SRT preparation or substitution of one SRT for another formulation at the same dosage to achieve the most appropriate regimen and dosing interval for asthma patients.