LITERATURE REVIEW

Theophylline

Theophylline is a naturally occurring alkaloid found in tea and is structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. The molecular formula of anhydrous theophylline (1,3-dimethylxanthine) is $C_7H_8N_4O_2$ with a molecular weight of 180.17[26] (Figure 1).

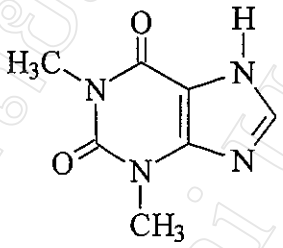

Figure 1. Structural formula of anhydrous theophylline

In early 1970 theophylline has traditionally been classified as a bronchodilator and has been used as a preventive agent for chronic asthma[27;28]. The drug has two distinct actions in the airways of patients with reversible obstruction including smooth muscle relaxation (i.e., bronchodilation) and suppression of the response of the airways to stimuli (i.e., non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III and to a lesser extent, PDE IV). While non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms that do not involve inhibition of PDE III or antagonism of adenosine receptors. Some of the adverse effects associated with

theophylline appear to be mediated by inhibition of PDE III (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow). Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine mediated channel.

The absorption of theophylline from oral solution and plain tablets is rapid and maximal concentrations can be achieved within 2 hours. Theophylline is eliminated primarily by metabolism in the liver. Its elimination rate is influenced by a number of variables such as genetic factor, age, smoking, concomitant medications and disease status, therefore there is marked interindividual variation in the rate of elimination. Its average half-life in nonsmoker adult is approximately 8-9 hours, however its half-life can be as short as 3-4 hours in young children and in patients who smoke. Subsequent studies show that the benefits and risks of theophylline relate directly to its plasma concentration[29;30] and monitoring of drug levels is required. Oral plain tablet preparations are no longer in common use because they require frequent dosing and do not provide constant blood levels. Moreover they produced wide differences between peak and trough serum concentrations. Oral SRT formulations have been developed to compensate for its rapid absorption and elimination[12]. The SRT formulations provide slower and continuous release of theophylline, resulting in consistent absorption and less fluctuation in plasma concentrations. They are designed for dosing intervals of 12 to 24 hours, which are suitable for long term use. By 1980, the SRT formulations have become leading medication for chronic asthma and other chronic obstructive lung diseases[2]. These formulations are useful in the treatment of moderate asthma and nocturnal asthma. Generally, the use of twice-daily dosing SRT will result in less peak-to trough fluctuation than the use of once-daily dosing. Moreover, patients with rapid elimination half-life of less than 5 hours (children, adults who smoke or take drugs

that enhance theophylline elimination) or patients required serum concentration above 10 μg/ml may have greater therapeutic efficacy from the twice-daily dosing schedule. Nevertheless, control of nocturnal asthma could be achieved by using once-daily dosing of the SRT preparations. The appropriate administration time is in the late afternoon to early evening[31;32]. When the proper dosages are determined, these products will maintain relatively even blood theophylline levels sufficient to prevent symptoms during the night.

Although the SRT preparations offer dosing convenience to the patients, a number of issues must be considered concerning its use[33]. First, these preparations may not release the active ingredient over the entire dosing interval in a zero-order fashion. Second, it is difficult to determine the elimination rate of theophylline. Since absorption of theophylline may continue for a prolonged period, terminal portion of the elimination curve may be difficult to identify. Third, complete bioavailability cannot be reliably obtained based on the pharmaceutical formulation and the sustained-release characteristic of the product. The ultraslow SRT products for once-daily dosing may have less bioavailability due to inability to retain the product in the gastrointestinal tract for complete absorption. Fourth, the concurrent ingestion of food may affect the absorption characteristics of these SRT. For example, the concurrent administration of Theo-24 with a high-fat meal can accelerate its absorption thereby increase in the percentage of drug absorbed along with the extent of absorption (dose-dumping effect) in the first 4 hours. Another factor is circadian rhythm or day-night differences in absorption.

The SRT formulations; Uni-Dur®, Theo-Dur® and Xanthium® are currently available in Thailand. Theo-Dur® is available in 2 strengths: 200 mg and 300 mg. It is a SRT designed for twice-daily dosing. Uni-Dur® and Xanthium® are ultraslow SRT products design for once-daily dosing. Uni-Dur® and Xanthium® are available as 200 mg, 400 mg and 600 mg, respectively.

Pharmacokinetics of SRT

Absorption

Theo-Dur®

In a multiple dose steady-state, 5-day study involving 14 nonfasting subjects with theophylline half-life of 5.8-12.3 hours. Theo-Dur® 300-500 mg doses produce mean C_{max} and C_{min} levels of 12.2 ± 2.0 and 10.2 ± 1.6 μg/ml, respectively when dosing in the morning and C_{max} and C_{min} levels of 11.6 ± 1.6 and 8.7 ± 1.8 μg/ml, respectively when dosing in the evening. The mean percent fluctuation ± SD over the AM dosing interval is 30.4 ± 12.9% and 33.7 ± 13.1% over the PM dosing interval. In the same subjects, Theo-Dur® product was given once daily in the morning in dose ranging from 600-1000 mg (same daily dose as for BID above). It produces a mean C_{max} and C_{min} of 14.4 ± 2.2 and 5.5 ± 2.0 μg/ml, respectively, and a mean percent fluctuation ± SD of 195.8 ± 106.0 % and 33.7 ± 13.1%. Average peak-trough differences over 24 hours were 8.9 ± 1.3 and 3.7 ± 1.2 μg/ml when Theo-Dur® was given once or twice daily, respectively. In both once-daily and twice-daily dosing regimens, Theo-Dur® exhibits complete bioavailability when compare to an immediate-release product. The rate and extent of absorption of theophylline from Theo-dur® administered in fasting and fed conditions are similar[34].

Uni-Dur®

Following the single-dose crossover study, administration of Uni-Dur® tablet to 20 healthy male subjects produces peak serum theophylline concentrations of 5.3 ± 1.3 μg/ml at 13.6 ± 3.7 hours and 5.2 ± 1.5 μg/ml at 17.1 ± 6.3 hours in fasting and nonfasting condition, respectively. Food does not affect time to peak concentration and extent of absorption of Uni-Dur® as evidenced by the similar AUC_{inf} values. The relative extent of absorption of theophylline from Uni-Dur® tablet in fasting and nonfasting subjects is 84.3% and 88.7% of the immediate-release theophylline tablets. In a multiple-dose, crossover study with 24 healthy nonsmoking male subjects having an average theophylline clearance of 5.70 ± 2.36 L/hr, Uni-Dur® tablet once daily in the morning for 5 consecutive days exhibited better extended-release characteristics compared with a reference extended-release product administered every 12 hours (2× 300 mg) in the same manner. The mean percent fluctuation is 130% for the once-daily Uni-Dur® regimen and 389% for the reference BID product. The extent of theophylline absorption from Uni-Dur® tablets is 74.9% relative to the reference product[34].

Distribution

Once theophylline enters the systemic circulation, about 40% is bound to plasma protein[1], primarily albumin. Unbound theophylline distributes throughout body water, but distributes poorly into body fat. The apparent volume of distribution is approximately 0.45 l/kg (range 0.3-0.7 l/kg) based on ideal body weight. Theophylline passes freely across the placenta, into breast milk and into the cerebrospinal fluid. Saliva theophylline concentrations approximate unbound serum concentrations, but are not reliable for routine or therapeutic monitoring unless

special techniques are used. An increase in the volume of distribution of theophylline, primarily due to reduction in plasma protein binding, occurs in premature neonates, patients with hepatic cirrhosis, uncorrected acidemia, and the elderly and in women during the third trimester of pregnancy.

Metabolism

Following oral dosing, theophylline does not undergo any measurable first-pass metabolism. In adults and children beyond one year of age, approximately 90% of the dose is metabolized in the liver. Biotransformation takes place through demethylation to 1-methylxanthine and 3-methylxanthine and hydroxylation to 1,3-dimethyluric acid. 1-methylxanthine is further hydroxylated, by xanthine oxidase, to 1-methyluric acid. About 6% of a theophylline dose are N-methylated to caffeine. Theophylline demethylation to 3-methylxanthine is catalyzed by cytochrome P-450 1A2, while cytochromes P-450 2E1 and P-450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P-450 1A2 or a closely related cytochrome[1] (Figure 2). In neonates, the N-demethylation pathway is absents while the function of the hydroxylation pathway is markedly deficient. The activity of these pathways slowly increases to maximal levels by one year of age.

Excretion

In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first three months of life, approximately 10% of the theophylline dose is excreted unchanged in the urine. The remainder is excreted in the urine mainly as 1,3-dimethyluric acid (35-40%), 1-methyluric acid (20-25%) and 3-methylxanthine (15-20%). Since little theophylline is excreted unchanged in the

urine and since active metabolites of theophylline (i.e., caffeine, 3-methylxanthine) do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children over 3 months of age. In contrast, the large fraction of the theophylline dose excreted in the urine as unchanged theophylline and caffeine in neonates requires careful attention to dose reduction and frequent monitoring of serum theophylline concentrations in neonates with reduced renal function[1].

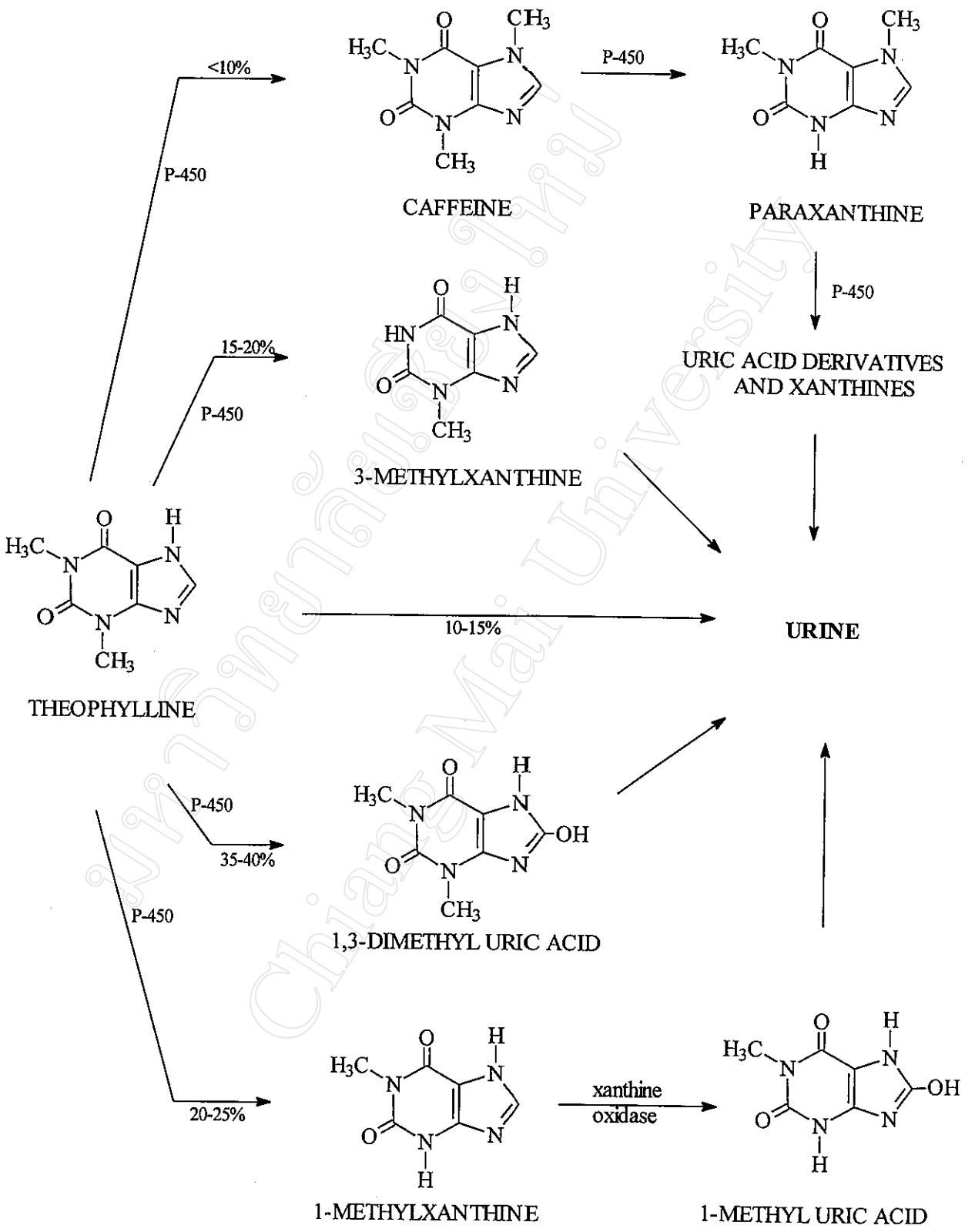

Figure 2. Pathway of theophylline metabolism.[35]

Adverse reactions

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are less than 20 μg/ml and mainly consist of transient caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. When peak serum theophylline concentrations exceed 20 μg/ml, however, theophylline produces a wide range of adverse reactions including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal[1]. The transient caffeine-like adverse reactions occur in about 50% of patients when theophylline therapy is initiated at doses higher than recommended initial doses (e.g., more than 300 mg/day in adults and more than 12 mg/kg/day in children beyond 1 year of age). During the initiation of theophylline therapy, caffeine-like adverse effects may transiently alter patient behavior, especially in school age children, but this response rarely persists. Other adverse reactions that have been reported at serum theophylline concentrations below 20 μg/ml include diarrhea, irritability, restlessness, fine skeletal muscle tremors, and transient diuresis.

The pharmacokinetics of theophylline varies widely among similar patients and cannot be predicted by age, sex, body weight or other demographic characteristics. In addition, certain concurrent illness and alteration in normal physiology and co-administration of other drugs can significantly alter the pharmacokinetic characteristics of theophylline. Within subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. It is, therefore, recommended that serum theophylline concentration be measured frequently in acutely ill patients, e.g., at 24-h intervals and periodically in patients receiving long-term therapy, e.g., at 6-12 month intervals. More frequent measurement should be made in the presence of any condition that may significantly alter theophylline clearance[1].

Asthma

Asthma is a pulmonary disease characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to variety of stimuli. It is manifested by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy[36]. Clinical manifestations consist of a triad of paroxysms of dypsnea, cough, and wheezing. The underlying pathogenesis of asthma is a nonspecific hyperirritability of the tracheobronchial tree to various stimuli[37]. The stimuli include allergens (e.g., domestic mites, animal dandruff, cockroach), air pollutants (e.g., ozone, nitrogen dioxide, sulfur dioxide), occupational factors (e.g., chemical irritants, wood and vegetable dusts, animal and insect dusts), respiratory tract infections, tobacco smoking, cold air, exercise, and emotional stress. Following exposure to an initiating stimulus, mediator-containing cells (mast cell, basophils, and macrophages) can be activated to release a variety of inflammatory compounds which produce direct effects on airway smooth muscle and capillary permeability[36;38]. The effects brought about are contraction of bronchial smooth muscle, vascular congestion, edema of the bronchial wall, and thick tenacious secretions. The results are narrowing of the airway, increase in airway resistance, and a decrease in forced expiratory volume and flow rate. Most people with asthma have a mild form of the disease with symptoms occurring occasionally. More severe forms are associated with frequent attacks of wheezing dyspnea, especially at night. Worsening of asthma during sleep is referred to as nocturnal asthma[36]. Nocturnal asthma symptoms are frequent; 39% of asthmatics reported nightly nocturnal awakening, 74% at least one night per week, and 94% at least one episode per month[39]. Nocturnal airway obstruction not only is a common and troublesome problem but is also potentially dangerous manifestation of asthma. Studies have shown a clustering of asthma death at night. In one survey of the timing of respiratory arrest or death from asthma, it was

found to occur in patients who had large variations in peak flows from morning to night. Thus, the individual with frequent nocturnal symptoms with large variations in pulmonary function may be particularly at risk for sudden death from asthma at night.

Although the pathogenesis of this phenomenon is unknown, it has been associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine[40]. More recent data suggest that numerous factors that can affect nocturnal worsening of asthma including exposure to dust mite allergen, late-phase allergic reaction, effects of posture and sleep stage on air way tone, gastroesophageal reflux, impaired mucociliary clearance, airway cooling, improper environmental control, sinusitis. While no single mechanism can explain these changes, circadian rhythms may be particularly relevant[39]. The previous studies suggested that the most important role of sleep in the pathogenesis of nocturnal asthma is to synchronize circadian rhythm of hormones or other neurally controlled factors that lead to bronchoconstriction[41]. The circadian rhythm may play an important role in permitting inflammation of the airway and subsequent bronchial hyperresponsiveness. Even normal lung function has a circadian rhythm. In healthy persons, peak pulmonary function occurs between 03.00 and 04.00 PM. About 12 hours later, the nadir of lung function is seen[42].

Bronchial inflammation in asthma is inflammation of a very special kind and is characterized by extensive infiltration of the mucous and submucosa by lymphocyte and especially, eosinophils. In addition, the bronchial mucosa is extensively damaged and shed completely, leaving the basement membrane nude. There is considerable evidence that the epithelium damage results from the action of toxic eosinophil granule proteins. Thus, asthma can be considered to be chronic desquamating eosinophilic bronchitis. In the patients with allergic asthma, airway inflammation has been found to be the result of the late phase of the IgE-dependent allergic reaction. After exposure to an allergen, inflammatory cells (first neutrophils

and then basophils, eosinophils, and lymphocytes) appear in the airways. Pulmonary mast cell activation not only provokes acute airway obstruction but, in some asthmatic patients, also increases asthma about six hours later. This reaction to antigen has been defined as late-phase asthma. Late-phase asthma is an important result of mast cell degranulation and is characteristic of a more chronic phase of disease with regard to both airway obstruction and responsiveness[42]. The most effective means of reducing bronchial hyperresponsiveness is the use of corticosteroids, which suppress virtually every step in the inflammatory response. Inhaled steroids have proved to be effective in reducing nocturnal asthma. Another therapeutic approach is to give a long acting bronchodilator, and oral slow-release theophylline preparations have proved to be more effective than oral slow-release beta-agonists. The recent observation that theophylline prevents the late response to allergen may be particularly relevant, because it implies that theophylline may provide some protection against the development of airway edema, which may prove to be an important but neglected mechanism underlying nocturnal asthma.