CHAPTER II

REVIEW OF THEOPHYLLINE

Physico-Chemical Properties (28)

Theophylline is a dimethylated xanthine. Its structure is similar to the other xanthine derivatives, i.e.,caffeine and theobromine, which are commonly found in coffee, tea, cola beverages and chocolate. Although it is present in natural sources, theophylline is available commercially by total synthesis.

Chemical name : 1H-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-,mono or anhydrous ; 1,3-Dimethylxanthine

Empirical formula : $C_7H_8N_4O_2\ H_2O$

Structural formula:

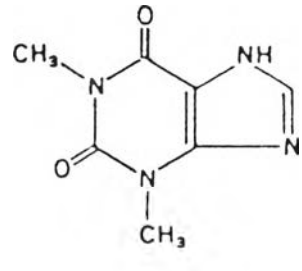

Figure 1. Chemical structure of theophylline

Molecular weight : Theophylline monohydrate 198.18
Theophylline anhydrous 180.17

Description : white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to litmus.

Solubility : 8.3 mg/ml in water, 12.5 mg/ml in ethanol, 11.6 mg/ml in chloroform, and freely soluble in solutions of alkali hydroxides and ammonia (29).

Melting range : 270 ^{o}C - 274 ^{o}C.

Stability : Theophylline is stable in air. Its solutions are generally quite stable over the entire pH range. Strongly alkali solutions (pH > 12) show decomposition after several weeks. Theophylline will precipitate from aqueous solutions if the pH drops below 9 unless present in concentration less than the water solubility.

Theophylline salts: A large number of basic salts and/or complexes have been prepared to increase the water solubility of theophylline for parenteral administration. The ethylenediamine salt (aminophylline) is the most widely utilized form of this drug for this purpose (29).

Pharmacological properties

Theophylline has several pharmacological actions. It can stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, and relax smooth muscle, notably bronchial smooth muscle (30,31).

1. Mechanism of action

Three basic cellular actions of theophylline have been studied to explain their diverse effects. They are 1) those associated with translocations of intracellular calcium, 2) those mediated by increasing accumulation of cyclic nucleotides, particularly cyclic AMP, 3) those mediated by blockade of receptors for adenosine. However, the concentration of free theophylline in plasma rarely exceeds 9 mcg/ml during therapy. This fact appears to limit the possible contribution of the first two categories of actions to the therapeutic effects of theophylline and leaves the anti-adenosine action as the leading candidate (30).

2. Efficacy

Theophylline is primarily used as a bronchodilator to treat acute or chronic asthma or bronchitis, though it has many other pharmacological

actions. From a study relating theophylline plasma concentration to its clinical response, the bronchodilator effect of theophylline was clearly demonstrated to vary directly with the logarithm of the plasma concentration (2). However, the therapeutic plasma concentration range of this drug was controversial.

The theophylline therapeutic plasma concentration range is commonly stated to be either 5 to 20 mcg/ml or 10 to 20 mcg/ml. These results were obtained from several investigations (2,7-9,32,33). Two studies conducted by Mitenko (2) and Maselli (32) reported the improvement of pulmonary function after intravenous administration of theophylline over the plasma concentration range from 5 to 20 mcg/ml. On the other hand, other studies conducted with oral administration reported that the plasma theophylline concentration in the range of 10 to 20 mcg/ml have been efficacious in relieving bronchoconstriction (7-9). The inhibition of exercise-induced bronchospasm also occurred at plasma theophylline concentration greater than 10 mcg/ml (33). The difference in therapeutic range estimation among these studies, however, may be associated with the variable factors in each study such as diagnosis of disease, disease severity, subjects' ages, and concomitant drugs, as described by Powell (34). However, the therapeutic range of plasma theophylline concentrations has generally been accepted to fall in between 10 and 20 mcg/ml (1,5,6,12-14).

3. Adverse effects and toxicity

Previous studies clearly demonstrated that theophylline toxicity was directly associated with its plasma concentrations (4-7). Severity and incidence of toxicity were both increased with plasma theophylline concentrations. Zwillich et al (5) reported a mean plasma theophylline concentration of 53 mcg/ml in a group of patients with seizures, compared to 35 mcg/ml in those with less severe toxicity and a mean concentration of 19 mcg/ml in patients without toxic symptoms. They also noted that among 8 patients with seizures, only one patient complained of prior nausea. Consequently, they and the other investigators (4,6) claimed that nausea and vomiting must not be used as clinical endpoints in dosage adjustment.

The incidence of toxicity increased with plasma concentration was shown by the study of Jacob and his co-workers (4). Toxic reactions occurred in 75% of patients with plasma theophylline concentrations over 25 mcg/ml, but were uncommon between 15 and 25 mcg/ml. They were absent when the concentrations were below 15 mcg/ml (4). They also reported an increasing frequency of adverse effects incidence as plasma concentration rose above 20 mcg/ml. This was supported by the other investigators (5-7). The concentration under 20 mcg/ml was accepted to be safe by these investigators (4-7). Adverse effects associated with plasma concentrations above 20 mcg/ml

included nausea, vomiting, diarrhea, abdominal pain, headache, irritability, and insomnia (4,7). Seizures, brain damage, cardiac arrhythmias and death occurred at higher levels (above 40 mcg/ml) (5,6).

Pharmacokinetic studies in man

1. Absorption

Theophylline was readily absorbed after oral, rectal or parenteral administration. The absorption of theophylline from a solution or from uncoated tablets was rapid and complete (35). Hendeles et al (36) reported that the absolute bioavailability of a theophylline solution in 5% ethanol averaged 99%, whereas that of an uncoated anhydrous theophylline tablet averaged 96%. The peak plasma concentrations were at 1.4 $\pm$ 0.4 hours and 2.0 $\pm$ 0.3 hours, respectively. Enteric-coated tablets (37) and some slow-release formulations (35,38), however, have been reported to be erratically and incompletely absorbed. The absorption of theophylline from solid dosage forms have been found to be complete but may be slower when food was present (39).

2. Distribution

The apparent volume of distribution (V) of theophylline in normal, nonsmoking adult volunteers was reported by many previous studies. Chrzanowski et al. (40) showed that the averaged of the apparent volume of distribution was 0.54 L/kg with a range of 0.4 to 0.7 L/kg. This result was similar to those reported by other investigators (17,18,20,39,41,42).

Several studies demonstrated that the apparent volume of distribution tended to be larger in premature neonates (43), in patients with chronic obstructive lung disease and arterial blood acidaemia (44) and in patients with hepatic cirrhosis (22). On the other hand, smaller apparent volume of distribution was observed in obese subjects (45), and in patients with chronic obstructive lung disease and arterial blood alkalaemia (44). However, the factors of smoking status, sex (17), age, asthma, congestive heart failure, pneumonia, severe bronchial obstruction (21) or acute pulmonary edema (20) did not affect the apparent volume of distribution of theophylline. Koysooko et al.(46) reported that an average of 59% of theophylline was bound in plasma of healthy adults. Binding was decreased in premature neonates (43) and in patients with hepatic cirrhosis (22).

3. Metabolism

Jenne and co-workers (47) demonstrated that theophylline was eliminated by biotransformation in the liver and by urinary excretion. Approximately 90% of theophylline was metabolized in the liver. The main excretory products in urine were 1,3-dimethyluric acid (39.6 ± 4.5 %), 1-methyluric acid (16.5 ± 3.3 %), 3-methylxanthine (36.2 ± 7.3 %), and unchanged theophylline (7.7 ± 6.1 %), similar to those previously reported by Cornish et al. (48). They also noted that theophylline was metabolized to uric acid derivatives via oxidation and to 3-methylxanthine via demethylation.

Monks et al. (49) indicated that theophylline, 1,3-dimethyluric acid and 1-methyluric acid were eliminated by first-order processes, while the elimination of 3-methylxanthines was eliminated by a process described by Michaelis-Menten kinetics. The metabolism and elimination of theophylline was influenced by dietary methylxanthines. Abstention from methylxanthine -containing foods and beverages led to increase in the elimination constants of theophylline and its three major metabolites.

4. Plasma clearance and elimination half-life

Previous findings of several investigations have demonstrated a poor correlation between dose and

plasma concentration of theophylline. This resulted from a wide variation of theophylline clearance rate among individual patients, expected to be caused by genetic differences (4,6,7,11-14).

In addition to genetic differences among individuals, there are several factors which apparently modify the individuals' ability to eliminate theophylline. As identified by Jusko et al. (10), the primary important factors for determining theophylline clearance include age, smoking status, liver disease and congestive heart failure. Several investigators observed that theophylline clearance was markedly reduced in premature neonates (43), infants under 6 months of age (25), acute ill adults with hepatic cirrhosis (22), cardiac decompensation (20,21) and cor pulmonale (50). In contrast, its clearance was increased in children (11-14), cigarette smokers (15-19) and those who consume marijuana (18), or high-protein, low-carbohydrate diet (39).

Some investigations (17-19) showed the clearance values for healthy-nonsmoking adults in the range of 0.026 to 0.094 L/kg/hr (mean 0.04 L/kg/hr) and average plasma elimination half-life value of 8 hours. However, there have been other reports which do not agree. Mitenko and Ogilvie (41,42) showed similar range of plasma clearance but shorter half-life values of approximately 4 hours, whereas Chrzanowski (40) reported a clearance in range of 0.052 to 0.200 L/kg/hr with longer average elimination half-life of 11.02 hours.

In children, theophylline clearance rate was significantly higher than in adults (11-14). Ellis et al. (11) reported the plasma clearance rate in 30 asthmatic children, 6-17 years of age, ranging from 0.031 to 0.221 (mean 0.087) L/kg/hr with elimination half-life ranging from 1.4 to 7.9 hours (mean 3.7 hours). These results were similar to those from other published reports (3,12-14). The study in Thais, Tuchinda et al. (25,26) observed that theophylline elimination half-life in Thai asthmatic children (8-13 years of age), ranging from 6.8 to 17 hours, was longer than that in Caucasian subjects. Therefore, race may be one of the factors which affects theophylline clearance.

The effect of smoking in theophylline elimination rates has been widely studied (15-19). The studies of Powell (17), Jusko (18), and Grygiel (19) indicated that the smokers had significantly higher theophylline clearance values (mean 0.06 L/kg/hr) with shorter elimination half-life values (approximated 5.5 hours) compared with nonsmokers. Jenne (15) and Hunt (16) also reported shorter elimination half-life ($t_{1/2}$ = 4 hours) in smoker group than in nonsmokers ($t_{1/2}$ = 7 hours). Smokers, in all studies (16-19), were defined as persons who smoked at least one pack of cigarettes (20 cigarettes) per day except in the study of Powell et al. (17), which defined smokers as persons who smoked at least 15 cigarettes per day. Nonsmokers were defined as persons who had never smoked or smoked only once or twice in their

lives, but Hunt et al. (16) included persons who had not smoked for at least 2 years. However, it has been found that data from both subject groups were indistinguishable. Also, Powell et al (17) reported that theophylline clearance rate and elimination half-life were not significantly different between nonsmokers and ex-smokers (persons who have quit smoking for the past 2 years). However theophylline clearance and elimination rate constant of ex-smokers tended to be greater than those of nonsmokers.

There are a few reports specifically studying effect of sex on disposition of theophylline. Study in adults, Powell et al. (17) found no significant effect of sex on theophylline clearance, elimination rate constant or apparent volume of distribution. This result was supported by the study of Jusko et al (10). Also, Hendeles et al (23) showed no effect of sex on theophylline clearance in children. On the other hand, both studies from Jusko (10) and Leung (24) have demonstrated the significantly higher clearance in young males than in young females (age in range of 6 to 19 years). In contrast, a study on factors affecting theophylline toxicity in critically ill patients suggested that male patients should received lower dose than female patients (6). This controversy created a question of whether both sexes required the same dose of theophylline.

Usual Dosage of Theophylline (51)

1. Oral- Standard rapidly absorbed oral formulation : Capsules, Tablets, and Liquids

For an acute attack not requiring parenteral therapy:

Usual adult dose Initially, 4.8 mg/kg followed by a maintenance dose of 2.4 mg/kg every six hours, adjusted as necessary to control symptoms with a usual optimal dosage of approximately 4.8 mg/kg every six hours.

Usual pediatric dose Initially, 6.4 mg/kg followed by a maintenance dose of 4 mg/kg every six hours, adjusted as necessary to control symptoms with a usual optimal dosage of approximately 6.4 mg/kg every six hours.

Note: The oral liquids are recommended for use in acute attacks since they produce therapeutic serum levels more rapidly than the solid dosage forms.

2. Oral- Extended-Release Tablets or Capsules

Usual adult dose Initially, 4 mg/kg every eight to twelve hours, adjusted as necessary up to 8 mg/kg every eight hours.

Usual pediatric dose see usual adult dose.