CHAPTER II

REVIEW OF LITERATURE

Theophylline

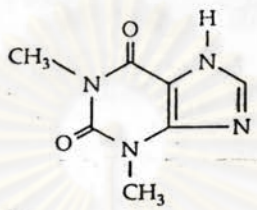

Figure 1 Structural formula of theophylline

Theophylline is 1,3-dimethylxanthine or 3,7-dihydro-1,3-dimethylpurine-2,6 (*1H*)-dione. It is a xanthine derivative bronchodilator.

1. Physicochemical Properties

(Martindale, 30th; BP 1988; The Merck Index 11th ed.)

1.1 Empirical formula $C_7H_8N_4O_2$

1.2 Molecular weight 180.17 (C 46.66%, H 4.48%, N 31.10%, O 17.76%)

1.3 Characteristics A white odourless crystalline powder. Bitter taste.

1.4 Solubilities Soluble 1 in 80 of alcohol

Slightly soluble in water (more

soluble in hot water) and about 110 in chloroform

Very slightly soluble in ether

Dissolvesinsolutionsofalkali

hydroxides, in aqueous ammonia, and in mineral acids

Dil in HCL or HNO_3

1.5 Light absorption

Ultraviolet absorption -UV max (0.1 N Hydrochloric acid and 0.01 N Sodium hydroxide) 272 nm (E 1%, 1cm = 530), 277 nm (E 1%, 1 cm = 650)

Infrared absorption -major peaks are at 744, 1189, 1445, 1565, 1665 and 1710 cm^{-1}

1.6 Melting point approximately 272 ^{0}C (270-274 ^{0}C)

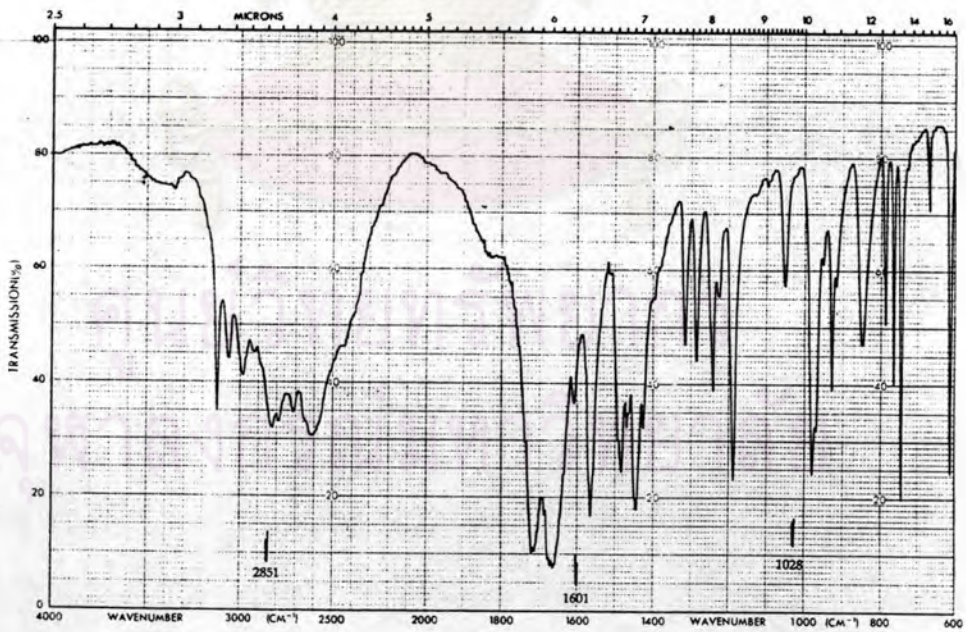

Figure 2 Infrared spectra of theophylline

1.7 pka at 25 ^{0}C : 8.77

1.8 pkb 13.5, 11.5.

2. Pharmacology

Theophylline is a dimethylated xanthine similar in structure to caffeine and theobromine, which are found in coffee, tea, cola beverages, and chocolate. Although theobromine was recently demonstrated to produce similar bronchodilation in a single-dose study, theophylline is currently the only xanthine marketed in the United States of America that has been demonstrated to be effective in treating chronic asthma. Diphylline, a 7 - dihydroxypropyl derivative of theophylline, is available, but several studies have shown it to have only 20% of the potency of theophylline; thus, it is not a variable alternative to theophylline.

Various substances have been added to theophylline either to increase its solubility (intravenous aminophylline) or to improve oral absorption. Since absorption of methylxanthines relates more to their lipophilic characteristics than to water solubility, there is no rationale for oral formulations that contain ethylenediamine, calcium salicylate, sodium glycinate, choline, or other bases aimed at improving water solubility (Iafrate, Massey and Hendeles, 1986).

The pharmacological effects of this drug on human organ systems are quite diverse, but usually predictable. Theophylline induces profound smooth muscle relaxation of the bronchioles. The drug can also exert appreciable effects on the cardiovascular, renal, and central nervous systems.

2.1 Mechanism of Action

Theophylline probably works by inhibiting phosphodiesterase, which, subsequently, impairs breakdown of cyclic 3´-5´ adenosine monophosphate (cAMP), resulting in intracellular accumulation of cAMP, as shown in figure 3. (Baptista and Driscoll, 1984; Glynn-Barnhart, Hill, and Szefler, 1988; Lesko, 1979)

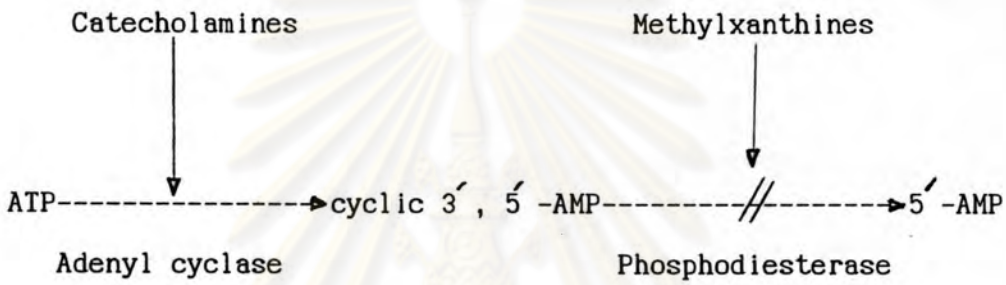

Figure 3 Suspected mechanism of action via the pathway of cyclic 3´,5´-adenosine monophosphate (cAMP) metabolism, resulting in the accumulation of cAMP. (Roberto, German and Elliot, 1970)

This mechanism has been questioned, however, since the concentrations of theophylline necessary to significantly inhibit phosphodiesterase would result in a high incidence of adverse effects. Also, some drugs that show significant phosphodiesterase inhibition (i.e., dipyridamole, paparerine) are incapable of inducing dilation of the bronchioles.

Other suggested mechanisms include prostaglandin antagonism, effects on intracellular calcium, increased binding of cAMP to cAMP-binding protein, and adenosine antagonism. In addition to effects on the lung, other related pharmacologic actions of theophylline

include an increasing of right and left ventricular ejection fraction and reducing of the fatique of diaphragmatic muscles, which may in turn decrease the work of breathing. Although the clinical relevance of these effects has not been demonstrated, some investigators have proposed that they may offer benefit for patients with chronic obstructive pulmonary disease who do not show a hyperreactive airway component to their disease.

There are recent data suggesting that a portion of the bronchodilator properties of theophylline may be attribute to a β-adrenergic effect on the airways resulting in smooth muscle relaxation. It appears that theophylline has some bronchoprotective action, since it does block the late asthmatic response to inhaled antigen in sensitised patients.

Adenosine, an endogenous neurotransmitter which produces bronchoconstriction in asthmatic patients, is directly antagonised at receptor sites by theophylline. A potential antiasthmatic effect of theophylline may be due to adenosine antagonism; however potent methylxanthine bronchodilator, enprofylline, lacks this effect.

To date, there has been no single antiasthma effect for theophylline that has been completely elucidated. In fact, several potential and perhaps interrelated mechanisms may be responsible for the potent antiasthmatic effect of theophylline.

2.2 Effect on Pulmonary

When bronchodilation is induced by theophylline in the asthmatic lung, forced expiratory volume (FEV) increases. Bronchodilatory potential is greatest when the drug is used in the treatment of reversible bronchospasm; in patients afflicted with

chronic obstructive pulmonary disease (COPD) or irreversible respiratory disease,.the bronchodilator effects of theophylline are minimal.

Theophylline also relieves pulmonary hypertension via dilation of pulmonary veins and arterioles. The mucociliary clearance of thick sputum achieved by theophylline seems to be associated with increased transport of water and ions into the lumen.

Tolerance to the pulmonary effects of theophylline is rare.

2.3 Effect on Cardiovascular

Theophylline induces modest dilation of the vasculature as well as appreciable positive inotropic and chronotropic effects. An insignificant drop in arterial blood pressure may occur.

2.4 Effect on Renal

Theophylline indirectly induces a mild, transient diuresis with initial therapy, increased renal perfusion may increase the glomerular filtration rate and, hence, urine volume. Additionally, inhibition of proximal tubular, reabsorption of sodium and chloride has been reported.

2.5 Effect on Central Nervous System

Theophylline mildly stimulates all levels of the central nervous system. This effect, however, is usually transient since tolerance develops rapidly. It may also increase resistance wihin the cerebral vasculature resulting in decreased perfusion. Interestingly,

its action as a medullary stimulant makes it effective for treating neonatal apneic episodes.

3. Pharmacokinetics

3.1 Absorption

Absorption characteristics of a dosage formulation are usually described by the rate and extent of drug absorption. Most commercial formulations of oral theophylline now available are well absorbed and rapid (Hendeles, Weinberger and Wighley, 1977; Upton et al., 1980), facilitating rapid achievement of therapeutic plasma concentrations. It is found that the absolute bioavailability of a theophylline solution in 5% ethanol in 20 asthmatic adults averaged 99% (range 88 to 112%) where as that of an uncoated anhydrous theophylline tablet averaged 96%. Peak plasma theophylline concentrations were absorbed at 1.4 $\pm$ 0.4 hours after administration of the solution and 2.0 $\pm$ 0.3 hours after the tablet.

The absorption on theophylline is dependent on disintegration and subsequent dissolution, the latter being the rate-limiting process.

Sustained-release preparations are intentionally formulately to retard dissolution, thus allowing for prolonged absorption and continuing therapeutic activity. Ingesting food along with theophylline has no appreciableeffect onthe absorption of most preparations, except with formulations whose dissolution is pH-dependent.

3.2 Distribution

Once theophylline enters the systemic circulation, about 40% becomes bound to plasma protein, the remaining free drug distributes throughout body water, the 60% protein binding reported in previous studies was artifactually elevated due to the low temperature and high pH conditions in vitro.

Theophylline follows a two-compartment model of distribution, in which the first component is the serum, while the bronchioles and other peripheral tissues comprise the second. After absorption, the drug is rapidly distributed that serum concentrations are in equilibrium with tissue concentrations of the drug wihin one hour after an intravenous injection. The apparent volume of distribution (V), the space into which theophylline distributes, ranges from 0.3 to 0.7 L/kg (30-70% ideal body weight) and averages about 0.45 L/kg in both children and adults. The mean volume of distribution for premature newborns and adults with hepatic cirrhosis or uncorrected acidemia, and the elderly is slightly larger since protein binding is reduced in these patients. In all other circumstances, even when theophylline clearance is altered, volume of distribution remains relatively unaffected.

Theophylline freely crosses the placenta and passes into breast milk although only minor adverse effects have been reported for infants indirectly receiving the drug in this manner. Theophylline crosses the blood-brain barrier more slowly than caffeine, but after distribution cerebrospinal fluid concentrations were reported to be approximately 90% of serum concentrations in premature infants. Concentrations in saliva average about 60% of serum levels.

3.3 Metabolism

The metabolism of theophylline in man has been described by several investigators and the generally accepted metabolic scheme is shown in figure 4. (Jonkman, and Upton, 1984; Lesko, 1979) If is metabolized via demethylation and the oxidative pathways in hepatic biotransformation. About 85% to 90% of a dose is metabolized probably in the microsomes of the smooth surface endoplasmic reticulum via a cytochrome P-458 or cytochrome P-450 dependent, mixed function oxidase system. The specific enzymes responsible for the metabolism of theophylline have not been identified. This occurs over multiple parallel pathways by both first-order and capacity-limited kinetic process. The major metabolite of theophylline, as depicted in figure 4, includes 1,3-dimethyluric acid, is formed by hydroxylation in the C-8 position, whereas 3-methylxanthine and the intermediate metabolite, 1-methylxanthine, result from N-demethylation. The intermediate metabolite, 1-methylxanthine, is rapidly converted by xanthine oxidase to 1-methyluric acid. Since the rate of formation of 1-methylxanthine is slower than its conversion to 1-methyluric acid, highly sensitive assays are able to detect only small amounts of 1-methylxanthine in blood and in urine. About 6% of a dose of theophylline is N-methylated to caffeine, which in turn is converted to paraxanthine. Available evidence suggests that N-demethylation and 8-hydroxylation pathway are mediated by two forms of cytochrome P-450, each with a distinctive substrate specificity (Tang-Liu, Williams, and Riegelman, 1982; Hendeles, Massanari, and Weinberger, 1986)

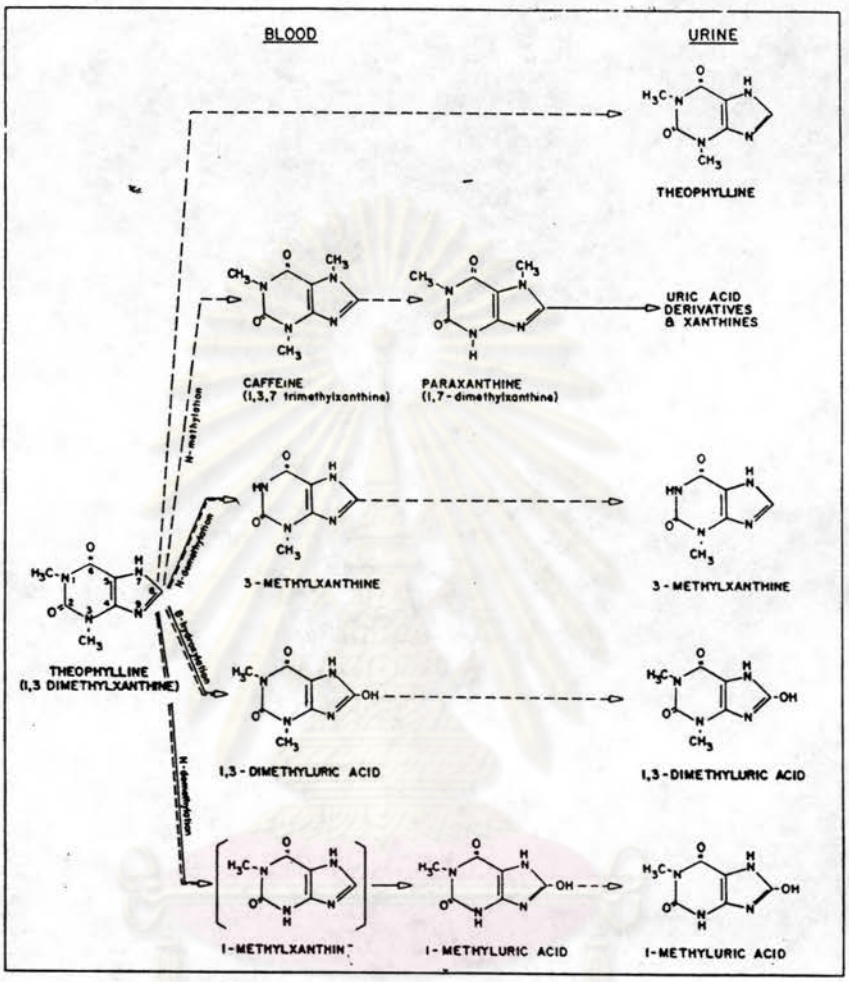

Figure 4 The generally Accepted Metabolic Scheme of Theophylline (Jonkman, and Upton, 1984; Lesko, 1979)

3.4 Elimination

Overall, theophylline and its metabolites are eliminated by parallel first order kinetics and Michaelis and Menton processes. About 10% of theophylline is excreted in unchanged forms by the kidney. As a result, increasing either the theophylline dosage or the competition for microsomal enzymes through ingestion of dietary xanthines can disproportionately affect theophylline metabolism and thus proportionally decrease the rate of clearance.

Hence, any increases in theophylline dosage should be incremental. Conversely, large increases in dosage made to achieve rapid therapeutic control may result in unexpected toxicity.

Furthermore, renal clearance of theophylline is also dependent upon urine flow rate, but less than 15% of a dose is excreted in the urine unchanged beyond the neonatal period. Therefore, dosage adjustments are not required in the presence of renal dysfunction, except in neonates during the first few months of life. In premature neonate, about 50% of the dose is excreted in the urine unchanged, and the remainder undergoes N-methylation to caffeine and C-8 hydroxylation to 1,3-dimethyluric acid. This increased metabolic activity commonly seen in children is most often attributed to an increased ratio of liver weight to body weight, resulting in increased relative amounts of microsomal enzymes.

The elimination half-life of theophylline approximates eight hours in non-smoking adults and four hours in children, However, significant variability exists and is most often attributed to individual differences in clearance rates.

3.5 Drug concentration

3.5.1 Therapeutic

In 1972, Jenne et al. first described the interpatient variation in theophylline elimination rate, dosage requirement, and serum concentration. A fixed dose of oral medication administered continuously to a group of asthmatic adults resulted in a wide range of serum concentrations within the 10-20 mcg/ml range, requirements varied from 400-2000 mg/day. A similar variability in rate of elimination was demonstrated for children, in whom the dose required to achieve a therapeutic serum concentration ranged from 16 to 40 mg/kg/day in the one to nine year-old age group. But serum levels as low as 5 mcg/ml may benefit some patients, who are often inadequate for stressful situations such as exercise or exposure to allergens. Importantly, the bronchodilatory potential to theophylline proportionally approximates the logarithm of the serum concentration within the range of 5-20 mcg/ml.

Fluctuations between C_{max} and C_{min} are usually greater when immediate-release dosage forms are used, and smaller with sustained-release products. Peak-to-trough differences in children who take immediate-release dosage forms average 9.2 mcg/ml, but up to 40% of children may show fluctuations greater than 10 mcg/ml.

Even sustained-release dosage forms, can induce considerable peak-to-trough differences. Ultimately, the degree of fluctuation depends on the rate of absorption of the individual product,the dosing interval, and the rate of elimination specific to the patient. Sustained-release dosage forms, however, offer the advantages of increased compliance, more consistent protection, and a lower

incidence of side and adverse effects.

3.5.2 Toxicity

Theophylline has the potential for a wide range of adverse effects. The toxic effects associated with very high serum levels are in reality exaggerated manifestations of the usual pharmacologic action. Magnified CNS excitatory phenomena include agitated maniacal behavior, hyperthermia, delirium centrally induced hematemesis, respiratory arrest, and seizures.

Focal and generalized seizures are perhaps the most frightening toxic reactions. They are more common in patients with serum levels of more than 40 mcg/ml.

Since seizures can occur without any obvious prior warning symptoms, serum level determinations are the only reliable means of forecasting their onset. Theophylline-induced-seizures respond poorly to anticonvulsants, and are also associated with a 50% mortality rate; serious brain damage is common among survivors.

Cardiovascular toxic effects include tachycardia, premature atrial and ventricular contractions, ventricular tachycardia, vascular collapse, and cardiac arrest. Cardiac toxicity is most often induced when serum levels exceed 40 mcg/ml.

4. Therapeutic indications

The main indication for theophylline is the relief of bronchospasm in asthma, bronchitis, and emphysema. Theophylline is also used to relieve apnoea in neonates. It was formerly used in the treatment of congestive heart failure, angina pectoris, and for its

diuretic action, but more effective agents are now available.

4.1 Asthma

4.1.1 Acute Severe asthma

Theophylline is not a first line drug in the treatment of acute severe asthma but may be used in adults and children who fail to respond adequately to oxygen therapy, β-agonists, and high-dose corticosteroids. The British Thoracic Society has recommended a dose of aminophylline 250 mg intravenously over 30 minutes but if an oral xanthine is already being taken, a β_2-agonist is preferred to avoid the risk of theophylline toxicity. If subsequent response to continued oxygen, a β_1-agonist, and corticosteroids is unsatisfactory an aminophylline infusion at a rate of 500 to 900 mcg per kg body-weight per hour is recommended. (British Thoracic Society, 1990)

4.1.2 Chronic persistent asthma

Oral xanthines should not be used as first line drugs in the treatment of chronic persistent asthma. Their main indication is in patients with symptoms, usually nocturnal, which are not controlled by high doses of anti-inflammatory agents and standard doses of inhaled β_2-agonists. The addition of a single nocturnal dose of a slow-release xanthine preparation may be adequate but a twice daily regimen may be necessary.

4.2 Chronic obstructive airways disease

In addition to its bronchodilating activity, theophylline may increase diaphragmatic contractility, suppress diaphragmatic fatique, and produce a modest improvement in cardiac performance in patients with chronic obstructive airways diseases such as chronic bronchitis and emphysema. Although some studies have demonstrated an improvement in lung function and exercise tolerance in such patients following theophylline or aminophylline administration, others have found no worthwhile benefit and it is generally recommended that theophylline should be tried only if symptoms of chronic obstructive bronchitis persist after the use of optimum doses of β_2-selective stimulants and antimuscarinics (Murciano, et al. 1984; Matthay, et al., 1982)

4.3 Erythrocytosis

Theophylline 8 mg per kg body-weight daily significantly reduced haematocrit, red-cell mass, and serum-erythropoietin concentrations during 8 weeks of treatment in 8 patients with erythrocytosis after renal transplantation. The need for weekly phlebotomy to lower the haematocrit was eliminated after one week of treatment with theophylline and it may provide an alternative to such phlebotomies in renal transplant patients. The adenosine- antagonist action of theophylline may be responsible for this effect as there is in-vitro evidence that the production of erythropoietin is modulated by adenosine (Bakris, et al., 1990).

4.4 Hyposmia

Theophylline is reported to be effective in the treatment of hyposmia and to act by increasing the receptor level of adenylate cyclase activity to stimulate olfactory receptor growth and sensitivity. Theophylline is particularly effective in type II hyposmia. Patients with type I hyposmia or anosmia commonly require the addition of systemic corticosteroids. (Henkin, et al.,1991)

4.5 Neonatal apnoea

Caffeine and theophylline are used in the treatment of neonatal apnoea. Caffeine has a number of advantages over theophylline including a wider therapeutic index, a more potent central respiratogenic effect fewer peripheral adverse effects, and a longer elimination half-life allowing once daily and less frequent monitoring of plasma concentrations. A comparison of theophylline (loading dose 7.5 mg per kg body-weight; maintenance dose 3 mg per kg three times daily) with caffeine at a standard dose (loading dose 12.5 mg per kg ; maintenance dose 3 mg per kg once daily) and at a higher dose (loading dose 25 mg per kg; maintenance dose 6 mg per kg once daily) in neonates of less than 31 weeks gestation with frequent apnoeic attacks found that theophylline and the higher dose of caffeine both produced greater improvement in apnoea within 8 hours. No adverse effects were associated with this high dose of caffeine, but in some neonates treated with theophylline dosage adjustment was necessary to reduce theophylline induced tachycardia. The use of caffeine was recommended in neonatal apnoea, but the lack of a readily availability precompounded stable preparation may limit its use. (Kriter, and Blanchard, 1989)

4.6 Neonatal respiratory distress syndrome

Aminophylline or theophylline has been used successfully to facilitate weaning of infants with respiratory distress syndrome or hyaline membrane disease from mechanical ventilation.

Aminophylline given ante portum to women at risk of premature delivery has reduced the incidence of neonatal respiratory distress syndrome and has been reported to be an effective as the anto partum administration of betamethasone. However, the administration of aminophylline to premature neonates did not significantly alter the course and outcome of respiratory distress syndrome. (Harris, et al., 1983)

4.7 Tremor

Although aminophylline has been reported to increase tremor in hyperthyroid patients and tremor may occur as a side-effect of theophylline treatment, aminophylline 300 mg daily by mouth for 4 weeks was found to reduce the severity of essential tremor in 20 patients. (Buss, et al., 1989; Mally, 1989)

5. Cautions

5.1 Contraindications

It is contraindicated in patients who have shown hypersensitivity to theophylline.

5.2 Precautions

5.2.1 The drug should be used with caution in patients with severe cardiac disease, hypertension, acute myocardial injury, congestive heart failure, cor pulmonale, severe hypoxemia, hyperthyroidism, hepatic impairment, or alcoholism, and in the elderly (especially males) and in neonates. Particular caution should be used in congestive heart failure. Reduced theophylline clearance in these patients may cause serum levels to persist long after the drug is discontinued.

5.2.2 This drug should be used cautiously in patients with a history of peptic ulcer since the disease may be exacerbated.

6. Effects in pediatrics, pregnancy and breast-feeding

6.1 Pediatrics

Information on safety and effectiveness in children under 12 years of age have not been established.

6.2 Pregnancy

It is not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Xanthines should be given to a pregnant woman only if clearly needed.

6.3 Breast feeding

Theophylline is secreted in breast milk and may cause adverse effects in the infant. Caution must be used when prescribing theophylline to a nursing mother, taking into account the risk/benefit of this therapy.

Long-term animal studies have not been performed with theophylline to evaluate carcinogenic potential, mutagenic potential, or effect on fertility.

7. Adverse reactions

7.1 Gastrointestinal

Nausea, vomiting, and diarrhea are the most frequently reported side-effects induced by theophylline. Although such effects can occur at serum levels as low as 13 mcg/ml, their incidence increases drastically when serum levels exceed 20 mcg/ml.

The effects of theophylline as a gastrointestinal irritant play some part in producing gastrointestinal symptoms, but central stimulation of emesis seems to be the most significant factor, Local irritation of the mucosa can often be alleviated by taking theophylline after meals; with a full glass of water. (Baptista, and Driscoll, 1984)

7.2 Central nervous system

Caffeine-like side-effects are fairly common when theophylline therapy is first started, but they tend to be transient. Although

there seems to be no direct relationship between CNS effects and serum level, these effects can often be minimized by initiating therapy with small doses, folowed by incremental increases when necessary. Nervousness, irritability, restlessness, tremor, insomnia, and headache are CNS effects that occur in patients over a wide of serum levels, but they surface more commonly in those whose serum level exceeds 20 mcg/ml.

7.3 Heart

Theophylline or aminophylline can precipitate arrhythmias at both therapeutic serum theophylline concentrations and overdose. Combined oral administration of theophylline with β-adrenoceptor stimutants does not increase the incidence of arrhythmias compared with the administration of theophylline alone but is associated with a significant increase in the mean heart rate.

7.4 Mental function

Several small studies have suggested that theophylline may be associated with learning and behavior problems in children, especially those with a low IQ. However, the FDA has concluded that such studies provide in sufficient evidence to support an adverse effect of theophylline on learning behavior or school performance. Other studies have found no marked behavioral side-effects that could be attributed to theophylline. Additionally, academic achievement generally appeared to be unaffected by either asthma or by treatment with appropriate doses of theophylline. (Weinberger, et al., 1987)

7.5 Skin

Hypersensitivity reaction include erythematous rash with pruritus, erythroderma, and exfoliative dermatitis. Hypersensitivity reactions to theophylline have been reported rarely but type I reactions have occurred. An erythematous, maculopapular rash has been reported during treatment with a sustained-release theophylline preparation which did not occur when aminophylline was given (Hardy , et al.,1983)

7.6 Urinary tract

Urinary retention has been reported in male patients during therapy with theophylline. (Owens, and Tannenbaum, 1981; Prakash, and Washburne, 1981)

7.7 Breasts

Gynecomastia occured in patient after one to two months of oral theophylline therapy and resolved within one month of discontinuation.

8. Drug interaction (Jonkman, Upton, 1984)

8.1 Caffeine

Removal of methylxanthines from the diet in adults led to faster elimination and more extensive metabolism of theophylline. However, the addition of extra methylxanthines to the diet did not

alter the disposition and clearance of theophylline. Even if a slight kinetic interaction between caffeine and theophylline does exist, its clinical importance is probably limited because most patients do not abruptly change the caffeine content of their diet.

8.2 Barbiturates

8.2.1 Phenobarbitone

Although it was not found to have a significant effect on the pharmacokinetics of theophylline, enhanced theophylline clearance.

8.2.2 Quinalbarbitone (Secobarbital)

It has been reported that 340% reversible increase in theophylline clearance in a child treated with an irregular schedule of doses of quinalbarbitone. This may, however, be attributable to an influence either analytically or kinetically by other drugs which were administered concomitantly, eg. sulphamethoxazole.

8.3 Carbamazepine

It has also been observed to increase theophylline elimination.

8.4 Phenytoin

Phenytoin can produced a 73% increase in theophylline clearance, however, the voloume of distribution of theophylline remained unchanged in both the healthy volunteers and the epileptic

patient.

Decreased oral absorption of phenytoin following concurrent theophylline administration has been decribed.

8.5 Cimetidine

Cimetidine inhibits the oxidative metabolism of theophylline reducing its clearance by 20% to 35% and prolonging in serum half-life, toxic effects have been reported. It has been recommended that the dose of aminophylline should be reduced by about one-third if cimetidine is used concomitantly. This inhibition of theophylline metabolism may be entranced by liver disease, but there is wide interindividual variation. The reduction in clearance may be greater in smokers. Studies have suggested that ranidine does not significantly inhibit theophylline metabolism,even at very high doses.

8.6 Allopurinol

Allopurinol 300 mg by mouth daily for 7 days was found to have no effect on the pharmacokinetics of theophylline. However, allopurinol 600 mg by mouth daily for 28 days has been found to inhibit the metabolism of theophylline and it is concluded that with concurrent allopurinol therapy, theophylline dosage might have to be reduced to avoid theophylline toxicity while the duration of allopurinol treatment, because it was longer, was more typical of that for patients than in previous studies, the daily dose was double that usually administered.

8.7 Macrolide antibiotics

8.7.1 Erythromycin

Although some investigators have not demonstrated an erythromycin / theophylline interaction, the majority of the literature on this subject indicates that in clinical practice an interaction can be anticipated. Within about 6 days of commencing concomitant erythromycin and theophylline therapy a reduction of about 25% in the theophylline dose may be desirable, preferably guided by plasma theophylline assay. In practice, an erythromycin course is 7 to 10 days; therefore theophylline dosage should almost always be reduced during comedication with erythromycin.

8.7.2 Triacetyloleandomycin (Troleandomycin)

The mechanism of this drug interaction is unknown; although triacetyloleandomycin is known to have hepatic toxicity, liver function assessed by serum enzyme activity was normal or almost normal in patients on the antibiotic. Nevertheless, 3 studies show a marked interaction necessitating a decrease of theophylline dose by about 50% in some patients also taking triacetyloleandomycin. Dose adjustment should be guided by plasma theophylline monitoring.

8.7.3 Other macrolide antibiotics

It is found that other macrolide antibiotics appeared to have no effect on the pharmacokinetic of theophylline.

8.8 Other antibiotics

8.8.1 Tetracycline and Cephalosporins

For tetracycline, it is reported that there is no reason for any major concern about the concomitant use of theophylline and tetracycline. Similarly, second generation cephalosporins do not have a significant influence on the clearance of theophylline when given in sustained-release form.

8.8.2 Amoxycillin / Ampicillin

It is concluded that the half-lives are not different.

8.8.3 Rifampicin (Rifampin)

Recent report, it is desribed a 23.3% decrease by rifampicin in the half-life of theophylline elimination. The clearance and the volume of distribution were both significantly increased.

8.8.4 Isoniazid

Isoniazid is a well-known inhibitor of the metabolism of many drugs, but its effection theophylline clearance is not well documented.

8.9 Sympathomimetic drugs (β-agonist bronchodilations)

A pharmacokinetic interaction between sympathomimetic drugs

and theophylline would be clinically important because these drugs are used concomitantly by many asthmatics. Unfortunately, only limited information is available.

8.10 ε-adrenoceptor blockers

Propranolol has been shown to inhibit antipyrine hydroxylation. It is shown that it also reduced theophylline clearance but the clinical importance of these findings may not be great since ε-blockers are preferably not given to patients with bronchial obstruction.

8.11 Antacids

Antacids are frequently taken with theophylline in order to avoid some of its long gastric effects, and biopharmaceutical interactions are especially conceivable. Different effects might be manifested with immediate, enteric-coated or sustained-release products, with different salts, or with preparations containing adjuvants with different physicochemical properties.

8.12 Corticosteroids

Corticosteroids are frequently included in the drug therapy of asthmatics. However, it is likely that no theophylline dosage adjustment is necessary during long term co-treatment with corticosteroids.

8.13 Diuretics

Diuretics are frequently employed in patients with pulmonary oedema and thus might be taken concurrently with theophylline. For furosemide, it is clear,that because of the contradicting reports, further studies on this interaction are needed.

8.14 Oral contraceptives

There is evidence that oral contraceptive steroids competitively inhibit hepatic mixed-function oxidases and therefore they can have an inhibitory effect on the biotransformation of drugs having a high metabolic clearance.

Some studies is reported that the use of oral contraceptive resulted in a decrese in theophylline clearance of about 28%. Thus half-life of elimination of theophylline was also significantly prolonged, but volume of distribution was similar.

8.15 Influenza vaccines

Influenza vaccination is recommended for patients suffering from chronic pulmonary disease. Many will be on long term theophylline therapy.

The findings suggest that the effect of influenza vaccination on theophylline clearance is absent or minimal, but until more detailed information is available, serum theophylline monitoring for at least 48 hours after influenza vaccination is recommended for patients with theophylline concentrations in the upper part of the therapeutic range.

8.16 Other drugs

8.16.1 Medroxyprogesterone Acetate

It is reported that medroxyprogesterone acetate has no significant effect on theophylline disposition in middle-aged patients with moderate to severe obstructive pulmonary disease.

8.16.2 Metoclopramide

Metoclopramide causes an enhancement of smooth muscle contractive activity, a decrease in gastric emptying time, and a decrease in gastrointestinal transit time. Therefore, the drug could theoretically have an effect on theophylline absorption, especially when the latter is given as a sustained-release dosage form. However, it is found no effect of metoclopramide on theophylline absorption when it was given concomitantly with Theo-Dur tablets.

8.16.3 Metronidazole

Metronidazole, a drug used for treatment of trichomoniasis, is-like the metabolic inhibitor cimetidine, a substituted imidazole derivative. Metronidazole mediated metabolic inhibition has been documented for some drugs. There were no significant in any of the pharmacokinetic parameters before and during metronidazole treatment.

8.16.4 Benzodiazepines

For retrospective study, it is concluded that there is a

tendency towards increased theophylline clearance in benzodiazepine users, but only 6 subjects were studied.

8.16.5 Verapamil

The calcium antagonist verapamil is being used with increasing frequency. Recently, decreased digoxin clearance during comedication with verapamil has been described. It is described that a patient with a strongly elevated theophylline concentration which have been caused by initiating of verapamil therapy. However, more studies on this possible drug interaction are needed.

8.16.6 Sulphinpyrazone

Sulphinpyrazone is a structural analogue of phenylbutazone, a drug known to have an effect on the metabolism of several drugs. The report is shown that administration of sulphinpyrazone resulted in a 22% increase of the total plasma theophylline clearance. This could have been the sum of increases in metabolic clearances by 3-methylation (32%), 1-demethylation (30%), and 8-oxidation (22%), and of a decrease in renal clearance (27%) of theophylline.

9. Factors altering theophylline disposition

In addition to expected genetic differences between individuals in plasma theophylline clearance, there are several factors such as age, body weight, diet, smoking habits, other drugs and diseases which apparently modify the individual's ability to eliminate theophylline.

9.1 Age

Premature neonates with theophylline, apnoea have extremely low plasma theophylline clearance values, presumably due to a developmentally deficient hepatic cytochrome activity resulted for N-demethylation of theophylline. Continuing infusions over several weeks have resulting progressive deseases in plasma theophylline concentrations suggesting either naturation of hepatic oxidative enzyme activity or self induction of biotransformation process.

For old age (more than 50 years old) did not change disposition of theophylline when other factors absent.

9.2 Sex

There are few reports specifically studying the effect of sex and none on the effects of use with of oral contraceptives, on the disposition of theophylline. A study of 28 healthy individuals demonstrated no effect of sex on theophylline clearance. One multiple regression analysis of risk factors for theophylline toxicity in critically ill patients suggested that female patients should receive lower doses than male patients. However, another has denied the need.

9.3 Body weight

The apparent volume of distribution for theophylline is reduced in obese subjects. The mean elimination half-life values were slightly longer in 14 obese subjects (8.6 $\pm$ 2.0 hours) compared with 57 normal volunteers (6.0 $\pm$ 2.1 hours), but when expressed in terms of ideal body weight, plasma clearance values in obese subjects (0.64

± 0.021 L/kg.hr^{-1}) were similar to those of normal subjects (0.063 ± 0.029 L/kg.hr^{-1}).

9.4 Diet

It has been observed that dietary methylxanthines commonly caffeine ingestion, interfered with the elimination of theophylline in 3 normal volunteers, 2 to 3 cups of coffee (with caffeine) resulted in peak plasma theophylline concentrations of over 170 ng/ml in 4 normal subjects suggesting that caffeine can be metabolized to theophylline. In 6 normal volunteers a change from usual home diet to low carbohydrate-high protein diets resulted in a decrease in the theophylline elimination half-life from 8.1 to 5.2 hours. A change to a high carbohydrate-low protein diet resulted in a theophylline elimination of 7.6 hours charcoal broiled foods with a high polycyclic carbon content can variable increase the rate of theophylline biotransformation in man.

9.5 Smoking habits

Non-smokers clearly have longer theophylline elimination half-life values and lower plasma clearance values than do heavy smokers of cigarettes or cigars. It is of interest that smokers of marihuana had similar theophylline clearance values as smokers of tobacco, but that smokers of both marihuana and tobacco have even higher clearance. Subjects who discontinued heavy smoking habit for at least 3 months, had theophylline half-lifes towards the non-smoking group. The average theophylline half-life of smokers who had discontinued their habit at least 2 years were intermittent between those non-smokers and

smokers and smoker groups.

Mild smokers (less than 10 cigarettes/day) who had discontinued their habit for a minimum of 3 weeks, had theophylline half-lives similar to those of a non-smoker group. The only negative study was in obese subjects in whom no difference could be discerned in theophylline half-lives or clearance between 7 smokers and 7 non-smokers.

Adverse reactions to theophylline have been reported to be reduced in smokers as compared with non-smokers, except in elderly patients. This raises the possibility that increasing age may decrease the responsiveness of hepatic drug metabolising enzymes to stimulants such as cigarette smoke. A major unanswered question is the time to recovery after induction of theophylline by smoking. A kinetic study of the effect of smoking on theophylline disposition in the elderly should be carried out as well as a study of the rate of recovery from the stimulated state upon cessation from smoking in a large and varied study population.

9.6 Diseases

9.6.1 Hepatic disease (Ogilvie, 1978)

Theophylline elimination is markedly depressed in patient with hepatic cirrhosis and theophylline toxicity is commonly associated with hepatic disease. Use of a nomogram in such cases has reduced the incidence of adverse effects, but there is considerable discussion on thility of specific measures of liver function as guidelines for further reduction of dosage.

9.6.2 Cardiac disease

In patients with pulmonary oedema, after intravenous aminophylline, it is found that peak theophylline concentration increased and theophylline clearance decreased. Even if reduced theophylline, increased toxicity has been reported in patients with congestive heart failure. The mechanism responsible for altered theophylline elimination in congestive heart failure or in pulmonary oedema is unknown. It is likely to be combination of hypoxemia, hepatic congestion, altered circulary flow, and theophylline disposition.

9.6.3 Pulmonary disease

There is no good evidence that uncomplicated asthma or chronic bronchitis per se alters theophylline clearance. The development of complications such as chronic obstructive pulmonary disease or pneumonia has been associated with reduced theophylline elimination. The mechanism for this reduction is not clear but may be due in part to associated hypoxemia and altered hepatic enzyme capacity. Most of these patients have received long term theophylline therapy which may alter the disposition of the drug because of mixed first order and Michaelis-Menten kinetics.

10. Dosage

Theophylline is available in oral dosage forms intended for administration every 4 to 6 hours. It is also available in a range of sustained-release oral preparations that only need to be administered

once or twice daily. Doses of theophylline are usually expressed as anhydrous theophylline. For sustained-release products, these are dosing recommendations.

Table 1 Oral Dosing of Theophylline*

Initial Oral Dosing*	#16 mg/kg/day or 400 mg/day, whichever is less, in all patients. #Infants, age 6 weeks to 1 year, may receive 8 mg/kg/day. #Increase in 25% increments, not more often than every 3 days.
Chronic Oral Dosing	#Infants -dose (mg/kg/day) = (0.3)(age in weeks)+ 8 #Children (1-9 years) -24 mg/kg/day. #Children (9-12 years) -20 mg/kg/day. #Adolescents (12-16 years) -18 mg/kg/day. #Adults -13 mg/kg/day or 900 mg, whichever is less.

* Dosage must be empirically modified in the presence of factors that affect theophylline clearance. Serum level determinations will serve to confirm appropriateness of adjustment.

** Not for acute therapy.