CHAPTER II

REVIEW OF LITERATURE

Review of Theophylline

1. Chemistry

Theophylline is 1, 3 dimethylxanthine which is a natural occuring alkaloid and structurally related to caffeine. Theophylline is poorly soluble in water, so that its lipophilicity is the primary factor determining the absorption of the compounds (Bertino, 1995).

Aminophylline or theophylline ethylenediamine is salt form of theophylline that is available either oral or parenteral preparation. It is a water soluble form of theophylline that is converted to theophylline approximately 80 % in vivo (Winter, 1994).

2. Pharmacology

Mechanism of Action

A primary pharmacologic action of theophylline is relaxation of smooth muscle and, in particular, broncial smooth muscle. The exact mechanism for this action has not been determined, but a number of possibilities have been suggested. Theophylline can stimulate the release of catecholamine, inhibit the enzyme phosphodiesterase resulting in an accumulation of cyclic AMP, block adenosine receptor activity, affect calcium modulation, and inhibit bronchoconstricting prostaglandin. Of these mechanisms, competitive antagonist at adenosine receptors is probably the most important effect at therapeutic serum theophylline concentration. Theophylline has a number of other pharmacologic properties. It is a potent stimulant of the central nervous system including the medulla respiratory center, a positive inotropic and chronotropic cardiovascular effect, enhance diaphragmatic contractility, and increase gastric acid secretion (Wahlig, Thompson and Sinaiko, 1992 ; Stork, Howland and Goldfrank, 1994).

In preterm infants, theophylline have been widely used for management of apnea of prematurity (Aranda and Turmen, 1979), adjunct in weaning infants from mechanical ventilation (Viscardi et al, 1985), and as part of the multidrug regimen in bronchopulmonary dysplasia (Rooklin et al, 1979). In apnea of prematurity, theophylline stimulates the central nervous system on various levels (O'Donnel, 1994) :

1. exciting CNS rhythm generator for respiratory control
2. increase chemoreceptor sensitivity to hypercarbia
3. improve ventilatory drive (not related to chemoreceptor sensitivity) and
4. stimulation of formation reticularis with increase alertness

For ventilator dependent preterm infants, the weaning from ventilatory assistance may be unsuccessful because of apnea, hypercarbia or progressive atelectasis. It has been suggested that as adjuvants to weaning, theophylline may act to improve pulmonary function by central stimulant to ventilation or to enhance diaphragmatic contractility and resistance to developing fatique of the respiratory muscle (Aubier et al, 1981).

In bronchopulmonary dysplasia, theophylline may be beneficial for decreasing airway resistance and increasing dynamic compliance by acting as bronchodilator (Rooklin et al, 1979).

3. Clinical Pharmacokinetics

3.1 Absorption

Theophylline is currently available in a number of dosage form. These forms include parenteral preparation, oral solution, oral rapid release tablets and sustained release tablets, and etc. Theophylline is rapidly and completely absorbed from the gastrointestinal tract after oral administration when disintegration or dissolution of the formular is not delayed. The absolute bioavailability has been shown to be approximately 1 (Hendeles, Weinberger and Bighley, 1977). However, the absorption of theophylline when given by mouth in neonates is hindered by several factors, including milk, relative achlorhydria, prolong gastric emptying time, or unpredictable peristalsis (Morselli, 1989). The recent report indicated that the bioavialability of oral theophylline in preterm infants is approximately 80% (Al-Omran and Al-Alaiyan, 1997). Peak concentration of plain

coated tablets occur generally 1.2 to 2.0 hours after administration (Bertino, 1995). The concurrent ingestion of food or magnesium containing antacids may reduce the rate but not the extent of theophylline absorption. Also, absorption of theophylline is influenced by circadian change. Investigations of chronopharmacokinetics have been documented after oral administration of the drug. It has been shown that slower absorption and consequently increase minimum serum concentration, tends to occur after nocternal administration of the drug, when theophylline is given at interval of 12 hours or longer (Troger and Mayer, 1995).

3.2 Distribution

After theopylline administration either oral or parenteral administration, it is distributed rapidly into systemic circulation. At therapeutic concentration, the protein binding of theophylline average about 60% but it is decreased to about 40% in newborn infants and in adults with hepatic cirrhosis (Serafin, 1996). The remaining free drug is distributed through body water. Concomitant with high plasma protein binding drugs can compete with the binding of theophylline. The free fraction of theophylline in plasma was increased by up to 18% when acetazolamide, cimetidine, furosemide, 4-hydroxycoumarine, pentobarbital, quinidine, diazepam, salicylic acid, sulfafurazole and valpoic acid were coadministered (Troger and Mayer, 1995). The protein binding of theophylline is concentration indepencent but pH dependent. The correlation between the changing in blood pH value and the plasma protein binding capacity of theophylline were reported. In vitro studied, the theophylline bound fraction increased from 30% at pH 7.0 to 65% at pH 7.8. The studies demonstrated that theophylline binding increase as the pH increase. The plasma protein content itself dose not influence protein binding capacity in the range of therapeutic theophylline plasma concentration (Richer and Lam, 1993).

Theophyline freely crosses the placenta and passed into breast milk. It crosses the blood brain barrier slowly into cerebrospinal fluid. Cerebrospinal fluid concentrations were reported to be approximately 90% of serum concentration in premature infants. Concentration in saliva average about 60% of serum concentration (Hendeles, Weinberger and Massanari, 1986).

3.3 Biotransformation

Theophylline is eliminated by hepatic biotransformation into mostly inactive metabolites that rapidly excreted in the urine. Up to 90% of theophylline in children and adults are eliminated by metabolism in liver, only 10% are excreted unchange via the kidney. Microsomal enzymes of the cytocrome P450 system appear to be responsible for biotransformation of theophylline (Bertino, 1995).

The metabolic pathway of theophylline is shown in figure 1. The first pathway of theophylline metabolism is 8-hydroxylation of parent compound to 1, 3 dimethyluric acid which represents 45 to 55% of total theophylline clearance. The second pathway of theophylline metabolism is N-demethylation. The results of these pathways of elimination are the formation of two metabolites : 1-methylxanthine which is further converted to 1-methyluric acid and 3-methylxanthine. 1-Methyluric acid and 3-methylxanthine account for 20-25% and 13-16% of the molar quantity of theophylline in the urine, respectively. The minor pathway of theophylline metabolism is converting to caffeine by N-methylation (Bierman and Williams, 1989 ; Stork et al, 1994).

In adults, approximately 10% of a given dose of theophylline is excreted unchanged in the urine. Neonates metabolize a large portion of theophylline to caffeine which the caffeine level approaches 25% of the serum theophylline concentration and 85% of the produced caffeine is renally excreted. In neonates, 50% of theophylline is excreted unchanged in the urine (Stork et al,1994). In older children and adults, the maturation of hepatic cytochrome P450 system results in an increase metabolites conversion to oxidated and methylated metabolites and a concomitant decrease in the percentage of circulating caffeine. However, theophylline clearance and the urine metabolites pattern in infants will reach adult values at 55 weeks' postconceptional age (4 to 5 months' postnatal age) and continue to increase after 60 weeks' postconceptional age (Kraus et al, 1993).

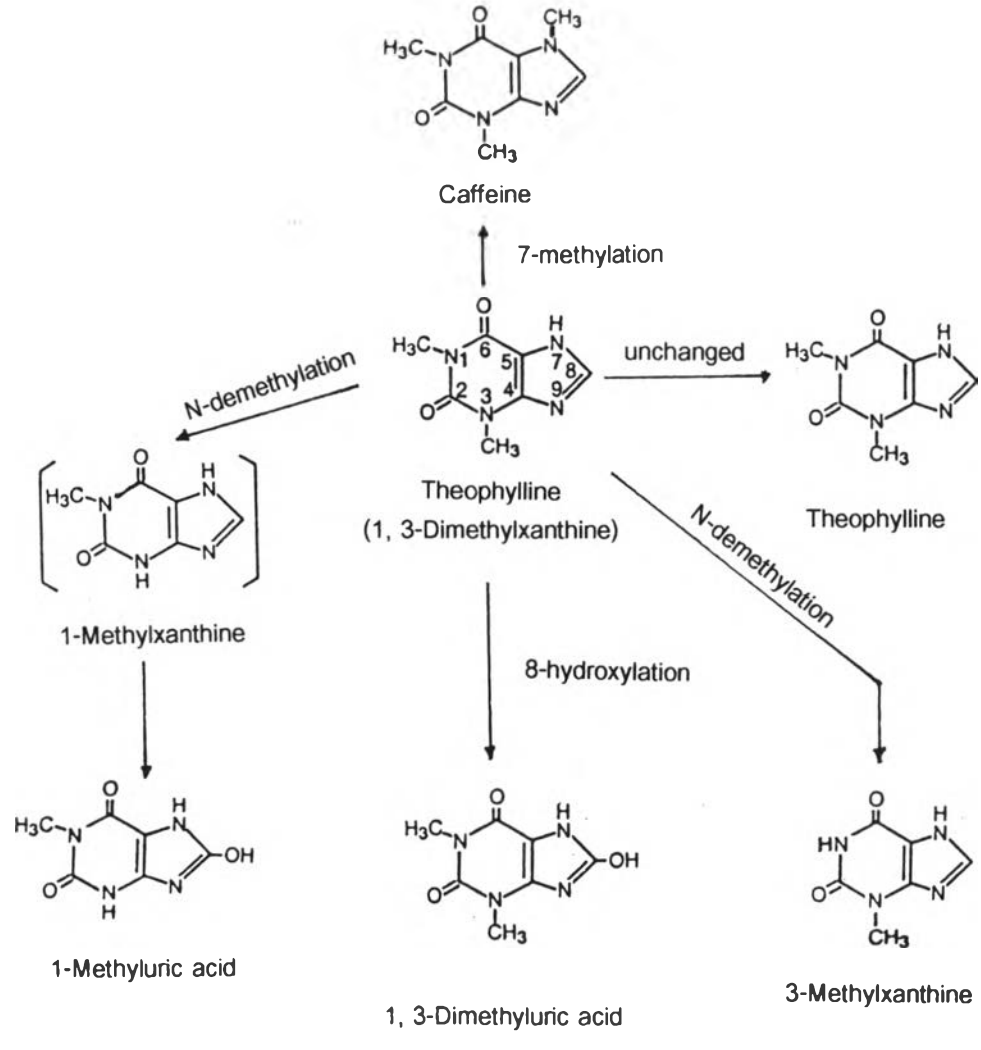

Figure 1 Theophylline biotransformation in humans

3.4 Pharmacokinetic Parameters

3.4.1 Volume of Distribution (Vd)

Vd is a parameter which is related to body weight. Because theophylline does not distribute into fatty tissue, appropnated weight should be ideal body weight (Jewesson and Enson, 1985).

Pharmacokinetic studies of population have shown that Vd is dependent on age. In neonatal period, the mean value of the Vd is about 0.69 L/kg (Aranda et al, 1992) whereas Moore et al (1989) reported the mean Vd was 0.858 L/kg. During the first 5 years of life, the Vd reduces to 0.4 to 0.5 L/kg similar to the Vd that usually occurs in adults.

Vd appears to have a high degree of correlation with arterial pH. Resar (1979) reported that arterial pH correlated inversely with the volume of distribution ($r = -0.824$, $p < 0.001$). Other studies reported an increase in the Vd when the level of plasma protein decrease. Alterations in plasma pH may change the degree of ionisation and distribution of drug. So that, plasma protein binding as well as pH are at least partly responsible for the variations in the Vd observed clinically (Richer and Lam, 1993). In addition, Vd may be influenced by different drugs, e.g. furosemide (Troger and Meyer, 1995).

3.4.2 Clearance (CL)

In neonatal period, the average theophylline clearance is 22 ml/hr-kg while the average theophylline clearance in adult is 66 ml/hr-kg (Aranda et al, 1992). Interpatient variability in clearance is large because of the difference in the rate of hepatic biotransformation which changes with several factors as age, concurrent illness, smoking, dietary intake and concomitant with other drugs.

Age : In preterm infants, theophylline clearance is lower than older children and adults because of immature of drugs metabolized organs. The capacity for biotransformation grows constantly due to developing liver maturity and attains adult values when the infants are approximately 6 months to 1 year of age. The capacity of the liver for biotransformation increases to its maximal level at approximately 3 to 5 years of age, and then decrease between the age of 8 and 16 year by more than 50%, finally reaching adult values (Troger and Meyer, 1995).

Concurrent illness : Birth asphyxia has been previously reported to result in a marked decrease in theophylline clearance in newborns (Gilman, Gal et al, 1986). Furthermore, diseases that influence liver function can have effects on theophylline biotransformation in a direct or indirect maner. Diseases that have a direct on liver function such as hepatic cirrhosis or acute hepatitis cause reduced clearance because of a loss of enzymatic capacity. In contrast, cardiovasculars diseases have indirectly influence on hepatic elimination. Example, left ventricular failure causes ischaemia of the liver because it cause hypoxia in liver (Troger and Meyer, 1995). In addition, Richer and Lam (1993) reported that theophylline clearance may be altered by changes in severity of the pulmonary obstruction, hypoxia and variation in arterial pH. In rabbits, hypoxia, hypercapnia and respiratory acidosis decreased total body clearance and led to increase the drug concentration.

Previous report demonstrated that viral infections caused a reduction in theophylline clearance by inhibition of the cytochrome P450 system (Chang et al, 1978). On the other hand, Muslow et al (1992) reported the lack of effect of respiratory syncytial viral infection on theophylline disposition in children. They recommended that theophylline dosing recommendation in RSV-infected children should not be altered, but careful monitoring of plasma theophylline level should be continued. Pneumonia was a disease state reported affecting on theophylline pharmacokinetics. Vozeh et al (1978) found the changing in theophylline clearance during acute illness. Theophylline clearance increased with resolving pneumonia. Disease state which affected on theophylline clearance are shown in table 1

Table 1 Concomitant diseases that affected on theophylline clearance

Hepatic disorders	Clearance
- Acute hepatitis	↓
- Cholestasis	↓
- Liver cirrhosis	↓
Cardiovascular disease	
- Congestive heart failure	↓
- Cor pulmonale	↓
Other disease	
- Viral infection	↓
- Hyperthyroidism	↑
- Hypothyroidism	↓
- Pneumonia	↓

↑ = increase ↓ = decrease

Smoking : The studies in adults found that smoking can markedly increase theophylline clearance. However, neonates whose mothers smoked during pregnancy do not have theophylline clearance significantly different than the values for neonates born to nonsmoker (Moore et al, 1989).

Diet : A high protein, low carbohydrate diet increase the rate of theophylline elimination because of inducing hepatic enzyme. Whereas a low protein, high carbohydrate diet decrease theophylline clearance compared to a normal diet (Winter, 1994).

In neonates especially preterm infants mostly receive nutritional supplement. Previous studies reported that infants receiving parenteral nutrition had a mean theophylline clearance that was 12% lower than those receiving breast milk or oral formula. This decrease in theophylline clearance might be expected since high glucose intake has been noted to inhibit drug metabolism in animal and the administration of parenteral nutrition has been associated with hepatic dysfunction in the newborn (Moore et al, 1989).

Drug interaction : Many drug interactions which influence on the theophylline clearance have been documents. Administration of these drugs with unchanged dose of theophylline results in increased or decreased plasma concentrations of theophylline, which may cause toxic symptomatology or inadequate clinical response.

The drugs that are commonly prescribed for pediatric patients which are known to interfere with theophylline metabolism are erythromycin, cimetidine and phenobarbital. Theophylline clearance decreases by mean of 25% after 6 day of erythromycin coadministration. The decreased theophylline clearance may be resulting from the inducing its own biotransformation into a metabolite that binds cytochrome P-450 into a hypoactive complex (Hendeles et al, 1986).

Cimetidine is a H_2 antagonist frequency used in infants. It is known to cause a decrease in theophylline clearance by mechanism of inhibition of hepatic microsomal mixed-function oxidase metabolism. Theophylline clearance decreases 23 to 100% (mean, 40%) when cimetidine coadministers. The effect begins in the first 24 hours of concurrent therapy (Hendeles et al, 1986)

Phenobarbital is the drug commonly used in preterm infants as prophylaxis against intraventricular hemorrhage and treatment of neonatal seizure. Previous study in adults had been reported that this drug increased theophylline clearance. The proposed mechanism

is induction of microsomal enzyme activity. However, this effect may take several weeks to occur and increases theophylline clearance by 11 to 60% (Hendeles et al,1986).

Additional drugs which are known to interfere with theophylline elimination are listed in the table 2. These drugs should be avoided in patients who are receiving chronic theophylline therapy. If absolutely necessary, the dose of theophylline should be decreased by one half and subsequently adjusted based on serum concentration monitoring.

3.4.3 Half life ($T_{1/2}$)

The half life of theophylline is about 30 hours in preterm and full term newborns, i.e. 5 times longer than that in adults, because of the immature enzyme system of the neonates (Aranda et al, 1992). Theophylline half life decreases when the liver maturity grows because of the increase in capacity for biotransformation. Children over the age of 1 year can have half lives as rapid as 2.5 to 4 hours (Bertino, 1995)

Table 2 : Drugs frequency used in infants and affected on theophylline clearance

Drug	Proposed mechanism	Effect
Carbamazepine	Induction of hepatic microsomal enzyme activity	Increases theophylline clearance by average of 60%.
Cimetidine	Inhibition of hepatic microsomal mixed - function oxidase metabolism	Decreases theophylline clearance by average of 40%. The effect begins in the first 24 hours of concurrent therapy.
Ciprofloxacin	Inhibition of hepatic microsomal enzyme activity (cytochromes CYP1A2 and CYP3A4)	Decreases theophylline clearance by approximately 30%.
Erythromycin	Induces its own biotransformation into a metabolite that binds cytochrome P450 into a hypoactive complex.	Decreases theophylline clearance by average of 80%. The effect occurs 6 days after concurrent therapy.
Pefloxacin	Inhibition of hepatic microsomal enzyme activity (cytochromes CYP1A2 and CYP3A4)	Decreases theophyline clearance by average of 30%.
Phenobarbital	Induction of hepatic microsomal enzyme activity.	Increase elimination by average of 25%.

Continued.

Drug	Proposed mechanism	Effect
Phenytoin	Increases activity of cytochrome P450 system involved in the metabolism of theophylline, while theophylline inhibits phenytoin absorption.	Increases theophylline clearance by average of 75%. The effect occurs 10 days after concurrent therapy.
Propranolol	Decreases N - demethylation of theophylline.	Decreases theophylline clearance by average of 20%
Verapamil	Alters the metabolism of theophylline by the liver to a small extent, as a result of which it loss from the body may be change. The P450 isoform CYP1A2 possibly has a small part to play in the verapamil interaction.	Decreases theophylline clearance by 8 - 20%.
Rifampicin	Induction of cytochrome P450 system.	Increase theophylline clearance by average of 80%. The effect occurs 14 days after concurrent therapy.

(Hendeles et al, 1992 ; Hendeles et al, 1986 and Stockley et al, 1994)

4. Adverse Drug Reaction / Toxicity

The most common adverse reactions associated with theophylline are gastrointestinal, cardiovascular and central nervous system side effect (Wahlig et al, 1992 ; Stork et al, 1994). Nausea and vomiting are the most common adverse effects in gastrointestinal system and these can occur even when the drug is administered parenterally. Nausea and vomiting commonly occur from direct central nervous system stimulation of the chemmoreceptor trigger zone as well as increased acid secretion and relaxation of lower esophageal sphinctor tone.

Central nervous system adverse effects, tremor and agitation, are due to catecholamine release. Seizure are usually a manifestration of cerebral constriction or central adenosine antagonists. It occurs in high theophylline serum concentration. Baker (1986) reported the occurence of seizure in children when the serum concentration is more than 30 mcg/ml.

Cardiovascular adverse effects such as cardiac arrhythmias are attributed to overstimulation of the myocardium and are associated with hypokalemia, hypophosphatemia and metabolic acidosis. Theophylline has been reported to lower the threshold for ventricular fibrillation. Other cardiac effects are pulse pressure widening, hypotension, and etc.

Other adverse effects such as hyperglycemia is the result of a stress response and catecholamine liberation. Hypophosphatemia and hypomagnesemia have also been noted but have not been defined mechanistically. The adverse reaction of theophylline may occur since the serum concentration were within therapeutic range. Children and the elderly may be particularly susceptible to the adverse reactions of theophylline, and drug concentration must be carefully monitored.

5. Theophylline Dosage Regimen

The recommendations of the Food and Drug Administration (FDA) in neonate consist of : (FDA, 1985)

Loading dose : Theophylline 1 mg/kg for every 2 mcg/ml desired increase in serum theophylline concentration.

Maintenance dose :

Preterm infants 40 weeks' postconception age (PCA) or younger : 1 mg/kg every 12 hours

Full term infants or more than 40 weks' postconception age : 1 - 2 mg/kg every 12 hours

However, the FDA recommendation of theophylline in neonates generally resulted in subtherapeutic serum concentration (Gillman and Gal, 1986). In clinical practice, Aranda et al (1992) recommended :

Loading dose : Theophylline 5 - 6 mg/kg

Maintenance dose : Theophylline 2 - 4 mg/kg/day in two to four divided dose

6. Theophylline Therapeutic Monitoring

Intravariability, intervariability, narrow therapeutic index, and the potential for serious toxicity have led to concern regarding theophylline usuage in children (Hendeles et al, 1992). The optimal theophylline serum concentrations are 6 - 12 mcg/ml for the patients with apnea and weaning and 10 - 20 mcg/ml for the patients with bronchopulmonary dysplasia because of the need for bronchodilating effect (Committee on Drugs, 1992 ; Shannon et al, 1975). However, some patients will tolerate higher concentration and a few will get a greater therapeutic level. So that, the serum concentration monitoring should be routinely performed or requires for patients taking theophylline who fail to exhibit benefit response while receive an appropriate dosage regimen, as well as, the patients who have an adverse reaction while on their usual dosage regimen.

6.1 Specimen Collection and Storage

Monitoring of serum drug concentration is best examined when two conditions for sampling are met :

1. Blood samples are drawn during the postdistributive phase for loading dose and maintenance dose.
2. Blood samples are drawn at steady state for maintenance dose when continue the same dose and dosing interval for approximately 3 - 5 half life (Winter, 1994)

The choice of sampling time does depend on the decision to monitoring concentration near the peak, trough, or some intermediate time. Theophylline sampling is somewhat controversial ; some clinicians recommend sampling for trough concentration, others recommend peak concentrations, while others accept peak and trough measurements. Blood sample for peak concentrations of intravenous should be obtained at 1 hour post dose (Schumacher, 1985). For solution and plain uncoated tablets with rapid dissolution characteristics, the peak occurs, on average, about 2 hours after the dose. For most slow release preparations, the peak occur approximately four hours after the dose. The addition, the trough concentration should be obtained at the end of the dosing interval (Hendeles et al, 1986)

Blood samples containing theophylline should be assayed as soon as possible when the blood samples are obtained. The containers contain blood sample may be used glass or polypropylene plastic container. Whole blood samples containing theophylline may be storaged for 1 day at room temperature (25 °C) or up to 3 days under refrigeration(4 °C) whereas serum samples containing theophylline may be storaged for up to three days at 25 °C , seven days at 4 °C , and 48 weeks when frozen at - 20 °C (Johnson et al, 1984).

6.2 Assay Methods

Available methods for determination of theophylline concentration in blood are gas liquid chromatography (GC), high performance liquid chromatography (HPLC), enzyme multiplied immunoassay technique (EMIT), radioimmunoassay (RIA), and fluorescence polarization immunoassay (FPIA). HPLC remains the method of choice in laboratories whose goal is extreme accuracy but it take long time for analysis (Bierman and Williams, 1989). A common assay method in clinical practice is FPIA because it is a rapid and reliable methods for therapeutic drug monitoring (Zaninotto et al, 1992). Oeltgen et al (1984) demonstrated that FPIA system offered greater sensitivity in the low drug concentration ranges while maintaining accuracy and precision comparable with those of established EMIT and RIA procedures.

The assay method used in this study was fluorescence polarization immunoassay (FPIA). FPIA uses two technologies to determine analyte concentration, competitive protein binding and fluorescence polarization. The fluorescence polarization results from the binding of fluorescein - labeled drug (tracer) to specific antibodies. If the specimen contains a high concentration of the

drug, the drug in the specimen can compete for the binding sites of antibodies more than the tracer molecules, leaving many tracer molecules unbound. The result is a decrease in the intensity of polarized light. If, however, the specimen contains a low concentration (or no concentration) of the drug, the tracer molecules can compete for the binding sites of antibodies more than the drug in the specimen, resulting in few unbound the tracer molecules. The result is an increase in the intensity of the polarized light.

6.3 Rapid Estimation of the Steady State Theophylline Serum Concentration based on the Drug Concentration during Non-steady state

Rapid adjustment for appropriate dosage regimen before the steady state serum concentration is reached is interested. The ability to achieve quickly and maintain therapeutic theophylline serum concentration while adequate benefit response and avoiding toxicity is essential to the successful use of the drug. Non-steady state, serum concentration methods, were used to evaluate patients pharmacokinetic parameters and led to the prediction of theophylline serum concentration during steady state. Pancorbo, Davies, and Raymond study (1981) evaluated the reliability of the basic equations in producing therapeutic theophylline serum level in adult patients (mean age 54.3 years). The average difference between predicted and measured theophylline serum concentration was -0.0055 mcg/ml with standard deviation of 2.67 mcg/ml. There was no significant difference between predicted and measured theophylline serum concentration.

Kurland, Chiou and Koup methods were evaluated in pediatric patients (mean age 3.1 $\pm$ 3.2 years, range of 5 months to 14.3 years). Kuland method based on single point and non-steady state theophylline serum concentration whereas Chiou and Koup methods based on two points and non-steady state theophylline serum concentration. Each method found the statistic significant of the correlation between predicted theophylline serum concentrations and measured theophylline serum concentrations during steady state (r = 0.68, 0.68, 0.68 respectively). Approximately 75 to 82% of predicted theophylline serum concentration were within 20% of the observed steady state value for all methods (Reiter, Hogue and Phelps, 1992). However, these methods has not been evaluated in the newborns.