CHAPTER II

REVIEW OF LITERATURE

Review of Theophylline

1. Chemistry

Theophylline is a dimethylated xanthine that is similar in structure to caffeine and theophylline that are found in coffee, tea, cola beverages and chocolate (lafrate and Blake, 1992). Theophylline , 1,3 dimethylxanthine, is a naturally accuring alkaloid and has limited solubility in aqueous solution (8 mg/ml at 25° C) (Ellis and Hendeles, 1986).

Aminophylline , USP is the complex of ethylenediamine and theophylline dihydrate (contains 80% anhydrous theophylline). Aminophylline has increased water solubility over theophylline , and there is commonly use for parenteral administration (Stratton, 1993).

2. Phamacology

The primary effect of theophylline seem to be to relax smooth muscle in both large and small airways (Barnes, 1992). Ellis and Hendeles (1986) described that theophylline has relieved acute symptoms of asthma, suppression of chronic symptoms of airway hyperreactivity and inhibition of exercise induced bronchoconstriction.

Nonbronchodilator respiratory effects that may be used to the patient with Chronic Obstructive Pulmonary Disease (COPD) include (1) improved diaphragmatic strength and reduction of fatigue, (2) stimulation of mucociliary clearance, and (3) improved central respiratory response to hypoxenia (Stratton, 1993). And theophylline may also improve cardiovascular performance in severe COPD by increasing in right and left ventricular ejection fraction and biventricular performance (Gotz, 1993).

Machanism of Action

Early studies suggested theophylline produce bronchodilation through inhition of phosphodiesterase thus preventing the enzymatic breakdown of 3' , 5' - c AMP. Later, numerous other mechanisms have been proposed to explain the mechanism of bronchodilation and other respiratory effects, including (1) inlibition of calcium ion inflex into smooth muscle, (2) prostaglandin antagonism, (3) stimulation of endogenous catecholamines, (4) adenosine receptor antagonism, (5) inhibition of release of mediators

from mast cells and leukocytes (Stratton, 1993), (6) prevention the development of microvascular leakiness as would an " anti-inflammatory" drug, (7) inhibition some function of T lymphocytes which may be relevant to control of chromic inflammation of the airway (Barnes, 1992).

3. Clinical Pharmacokinetics

3.1 Absorption

Theophylline absorption from liquids or plain tablets is rapid and complete, facilitating rapid achievement of therapeutic plasma concentrations. There is a great deal of variability in absorption characteristics among sustained release products in term of rate, also extent, and margin of absorption. This is of particular concern for a drug such as theophylline with a narrow margin of safety (Barnhart, Hill and Szefler, 1988).

Absorption of theophylline appears to be slower at night and follows a circadian pattern that results in higher morning trough levels for most slowly absorbed products. Nevertheless, slow - release products, if completely and reliably absorbed, allow longer dosing intervals with less fluctuation in serum concentration (Hendeles et al., 1986). Food alters the rate and extent of absorption of certain sustained release theophylline preparations as in the following Table 1 (Barnhart et al., 1988).

Table I : Effect of Food on the rate and extent of theophylline absorption from sustained release preparations.

Product (Trade Name)	Amount absorbed fasting (%)	Amount absorbed with food (%)	Rate of absorption with food	Clinical significance[a]
Twice daily preparations				
1. Theo-Dur Tablets	93	93	No effect	0
2. Somophylline-CRT	96	106	No effect	0
3. Slo-Bid Gyrocaps	85	85[b]	Slight decrease	0
4. Theo -grad	64	90	Decreased	+
5. Theolair - SR, Nuelin	ND[C]	No change[d]	Decreased	?
6. Theo-Dur Sprinkle Capsuls	91	44	Decreased	++
One - daily preparations				
1. Uniphyl, Uniphyllin	56	91[b]	Slight decrease	+
2. Theo-24, Pulmo-timelets	71	111[b]	6-8 hrs post dose marked increase	++

a : Clinical significance is anticipated by the magnitude of food-associated changes in the absorption characteristics and potential effect on theophylline monitoring (0 = no effect to , ++ = potentially significant effect).

b : Following administration with high - fat meal.

c : ND = no data available

d : Examined relative change to fasting state without inclusion of a reference product.

3.2 Distribution

Theophylline is rapidly distributed throughout extracellular fluids and body tissue with distribution equilibrium being reached 1 hour after an IV loading dose and intravenous injection (Barnhart et al., 1988; McEvoy, 1993). Theophylline in the systemic circulation is reversibly bound to plasma proteins average 40% of total drug concentration in normal and asthmatic subjects. In patients with hepatic cirrhosis and reduced serum albumin concentration, binding is reduced to approximate 30% to 35% , and in full - term neonates approximately one third of the drug is protein bound. Theophylline diffuses into breast milk, the cerebrospinal fluid, saliva, and presumably other body secretion (Ellis and Hendeles, 1986). The clinical significance of protein binding alternations has received little attention because theophylline is not highly protein bound and undergoes restrictive elimination in the liver. Increase in the fraction of unbound drug in the plasma does not change the unbound theophylline concentration. However, the total concentration will be lower in this situation. This could, in some patients, create an illusion of a subtherapeutic plasma concentration and lead to unnecessary and potentially dangerous dosage increases (Edwards et al., 1992).

3.3 Metabolism and Elimination

Berry et al. (1989) described that theophylline is primarily eliminated by metabolism via the hepatic cytochrome P-450 mixed - function oxidase microsomal enzyme with 10% or less excreted unchanged in the kidney or 10% to 15% of the overall excretion of theophylline in adults (Edwards et al., 1992). Each of the major metabolic pathways for theophylline is saturable within the usual therapeutic concentration so that theophylline frequently, though not always, exhibits nonlinear pharmacokinetic. This may partially explain in the relatively large intrapatient variability in theophylline clearance(often as great as 30%) over time. Part of the intrapatient variability in clearance is age dependent, with 1 to 9 years old having the greatest clearance rates, and therefore requiring the largest theophylline dosage. Pathway of theophylline elimination in adults and children was demostrated in Figure 1.

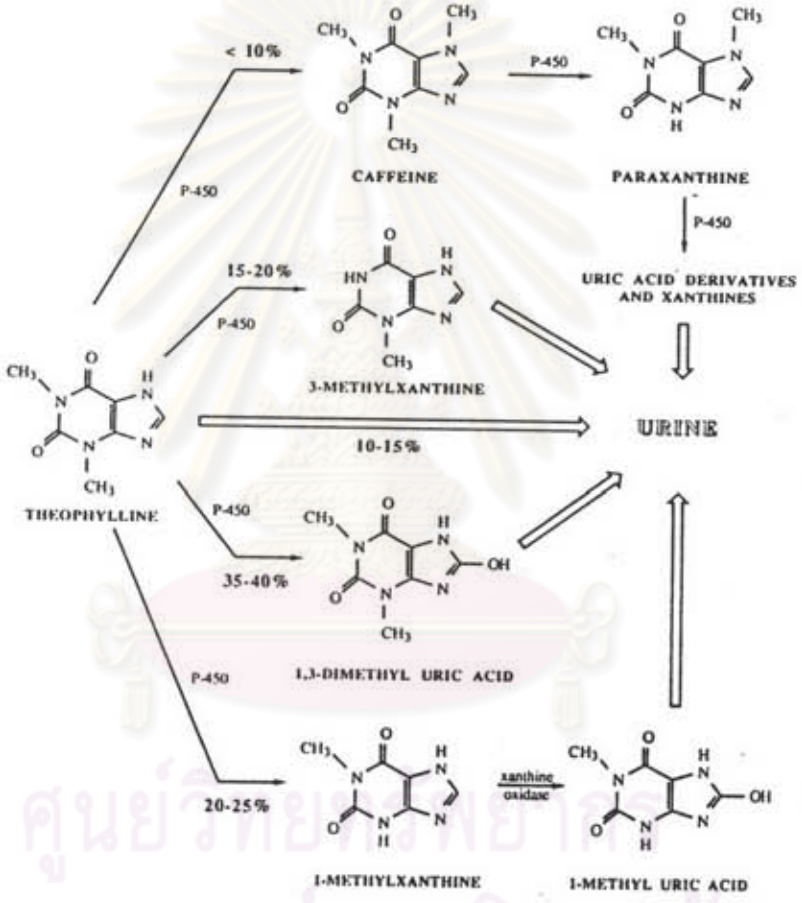

Figure 1 Pathways of theophylline elimination in adults and children. Solid arrows represent hepatic metabolism with enzyme involved and percentage of dose eliminated by each pathway being noted. Open arrows represent urinary excretion.

3.4 Pharmacokinetic Parameters

3.4.1 Volume of Distribution

The volume of distribution for theophylline is approximately 0.5 L/kg and distribution follow a two - compartment model. The volume of distribution in premature newborns is approximately 0.7 L/kg. After one year of age, however, the volume of distribution is approximately 0.5 L/kg. The FDA recommends that the ideal or non - obese weight be used to calculate the loading dose or volume of distribution, while others have suggested that use of total body weight may be more appropriate. This will result in a smaller volume of distribution and conservation loading dose. This approach may not be appropriate when calculating theophylline half - lives (Winter, 1992). Hendeles etal. (1986) reported that theophylline clearance was altered but volume of distribution remained relatively unaffected.

3.4.2 Clearance

The average theophylline clearance is 0.04 L/kg, based on lean or ideal body weight (Winter, 1992). Intrapatient variability in clearance is large and appears to be due to difference in rate of hepatic biotransformation, which changes with age, concurrent illness, smoking, aberrations in diet, and intake of other drugs. Available evidence suggests that there is no clinically important difference in theophylline clearance between obese and normal weight subjects or between males and females (Edwards, 1992; Hendeles et al., 1986).

3.4.3 Half - Life

The usual theophylline half - life in adult patients is approximately eight hours. The theophylline half - life can be as long as 18 - 24 hours in patients with severe congestive heart failure (Winter, 1992). Edward et al. (1992) reported that the half - life of theophylline was not influenced by the time of day.

3.5 Factors Affecting Theophylline Elimination

3.5.1 Hepatic Disease : Hepatic dysfunction is a major cause of altered theophylline biotransformation. Patients with decompensated cirrhosis, acute hepatitis, and possibly cholestasis, have reduced theophylline clearance (Slaughter, 1986 ; Staib et al. 1980).

3.5.2 Cardiac Disease : Cardiac disease (presumably causing decreased liver microsomal enzyme function by passive congestion of the liver secondary to congestive heart failure) may have a profound effect on theophylline metabolism (Hepner and Versel, 1978). With treatment of the heart failure, theophylline clearance increases (Ellis and Hendeles, 1986).

3.5.3 Fever : Fever, if sustained for > 24 hours slows theophylline elimination by an average of about 50% (Hendeles et al. 1992). If, fever is high and sustained (e.g.,> 102 F for 24 hours), dosage should be reduced in a patient who was previously maintained within the therapeutic range. (Ellis and Hendeles, 1986).

3.5.4 Pneumonia : Three adults with pneumonia and episodes of severe airway obstructive were reported to metabolize theophylline slowly, due to the hypoxemia associated with lung disease (Vozeh et al., 1978).

3.5.5 Diet : Ingestion a high protein, low carbohydrate diet accelerate theophylline metabolism, presumably by increasing liver enzyme activity (Winter, 1992). High protein diet increased theophylline clearance by approximate mean of 25% (Kelly and Hill, 1993).

3.5.6 Cigarette Smoking : This is a dose - related increase in theophylline clearance, with heavy smokers metabolizing theophylline twice as fast as nonsmokers, (Ellis and Hendeles, 1986).

3.5.7 Age : The data on the effect of advancing age on theophylline elimination are somewhat contradictory. Some authors report slower clearance in the elderly and others show no significant difference form young adults. In addition, protein binding may be decreased in the elderly which results in a lower free drug clearance rate. (Ellis and Hendeles, 1986). Edwards et al. (1992) compared the clearance between non - smoking subjectswith mean age of 27 and 72 years old to be 32% lower in the elderly subjects. Several other studies have found similar decreased in clearance (30% to 35%) over this age range with all metabolic pathways reduced to a similar extent.

3.5.8 Drug Interactions : Drug interactions are of major clinical importance. (Hendeles et al. 1986; Hendeles et al. 1992; Kelly and Hill, 1993;Winter, 1992).

Allopurinol (high dose : 600mg/day)

Effect : 25% mean decrease in theophylline clearance.

Mechanism : May be a nonspecific inhibition of hepatic microsomal enzyme activity.

Carbamazepine

Effect : Theophylline clearance increased by approximate mean of 50 - 60%

Mechanism : May be a result of induction of microsomal enzyme activity.

Cimetidine

Effect : Theophylline clearance decreased about 35 - 60% (mean 40%).

Mechanism : Inhibition of hypatic microsomal mixed - function oxidase metabolism.

Ciprofloxacin

Effect : Theophylline clearance decreased by approximate mean of 25 - 30 %.

Mechanism : Mechanism of drug interaction was not reported.

Erythromycin (Base and salts)

Effect : Theophylline clearance decreased by approximate mean of 25% after 6 days of concurrent therapy with enteric coated and ester.

Mechanism : In rats, erythromycin induces its own biotransformation into a metabolite that binds cytochrome P - 450 into a hypoactive complex.

Interferon (recombinant interferon alfa)

Effect : Theophylline elimination decreased by average of 50%.

Mechanism : Mechanism of drug interaction was not reported.

Isoproterenol (intravenous infusion)

Effect : Theophylline clearance increased about 6 - 42% (mean 19%)

Mechanism : Mechanism of drug interaction is unknow.

Norfloxacin

Effect : Theophylline clearance decreased by approximate mean of 10%

Mechanism : Mechanism of drug interaction was not reported.

Ofloxacin

Effect : Theophylline clearance decreased by approximate mean of 26%

Mechanism : Mechanism of drug interaction was not reported.

Oral contraceptives

Effect : 30% mean decrease in Theophylline clearance during chronic administration (may be less with low dosage).

Mechanism : May be as a result of microsomal enzyme inhibition.

Phenobarbital

Effect : Theophylline clearance increased by approximate mean of 25 - 34%.

Mechanism : May be a result of induction of microsomal enzyme activity.

Phenytoin

Effect : Theophylline clearance increased by approximate mean of 70 - 75% (additionally, theophylline apperars to inhibit absorption of phenytoin).

Mechanism : Presumably phenytoin increases activity of cytochrome P - 450 system involved in the metabolism of theophylline

Propranolol

Effect : Theophylline clearance decreased by approximate mean of 20 - 30%.

Mechanism : Mechanism of drug interactionis is unknow.

Rifampicin

Effect : Theophylline clearance increased an average of 79% after 14 days of concurrent administration. Interaction not reported in asthmatic patients.

Mechanism : probably due to induction of cytochrome P - 450 system.

Effect : Theophylline clearance decreased about 20 - 25%

Mechanism : Rifamipicin reduced theophylline metabolism.

Thiabendazole

Effect : Theophylline elimination decreased by average of about 65%

Mechanism : Mechanism of drug interaction was not reported.

Troleandomycin

Effect : Theophylline clearance reduced 41-59% (mean 50%)

mechanism : Mechanism of Troleandomycin is similar to Erythromycin.

4. Adverse Drug Reactions

The adverse effects of theophylline are extensions of the pharmacologic properties of the drug. As is true for bronchodilator activity, many adverse effects appear to be log - serum concentration related. Adverse effects may be categorized according to the organ system involved (Ellis and Hendeles, 1986; McEvoy, et al. 1993).

4.1 Gastrointestinal Effects : The most common adverse GI effects include nausea, vomiting, epigastric pain, abdominal cramp, anorexia and rarely dirrhea. Benett (1994) reported that nausea, vomiting, and epigastric pain generally were preceded by signs of nervous system stimulation.

4.2 Nervous System Effects : Adverse CNS effects inciude headache, irritability, restlessness, nervousness, insomnia, dizziness, reflex hyperexcitability and seizures. Seizures do not necessarily lead to death or irreversible brain damage if rapidly controlled.

4.3 Cardiovascular Effects : Adverse cardiovascular effects of theophylline include palpitation, sinus tachycardia, and increased pulse rate. These adverse cardiovascular effects are usually mild and transient. Flushing, hypotension, and ventricular arrhythmias may also occur. Ogilvie et al. (1977) reported that in therapeutic range, the effect of theophylline on increasing the heart rate was a modest one, in the range of 3 to 16 beats/minute.

4.4 Other Adverse Effects : Theophylline may also produce transiently increased urinary frequency, dehydration, and tachypnea.

5. Dosage

Multistep titration of dosage for adults and children over 1 years concluded in figure 2 (Bennett, et al., 1994; Hendeles et al., 1992). Algorithm algorithm for theophylline dosing in the adult patient with acute bronchospasm was also demostrated in Figure 3 (Edwards, 1992).

Figure 2 : Scheme for Establishing Multistep Titration of Dosage of Theophylline .

Initial dosage

Adults and children > 1 yr of age : 12 - 14 mg/kg per day up to a maximum of 300 mg/day

↓

After 3 days if tolerated, increase dose to:

Incremental dosage

Adults and children > 45 kg : 400 mg/day, children < 45 kg : 16 mg/kg per day up to a maximum of 400 mg/day

↓

After 3 days if tolerated, increase dose to:

Final dosage before serum concentration measurement

Adults and children > 45 kg : 600 mg/day

Children < 45 kg : 20 mg/kg per day up to a maximum of 600 mg/day

↓

Check serum concentration when no doses have been missed, added, or taken at unequal intervals for 3 days. The final dosage adjustment is dependent on the peak theophylline serum concentration and assessment of clinical improvement.

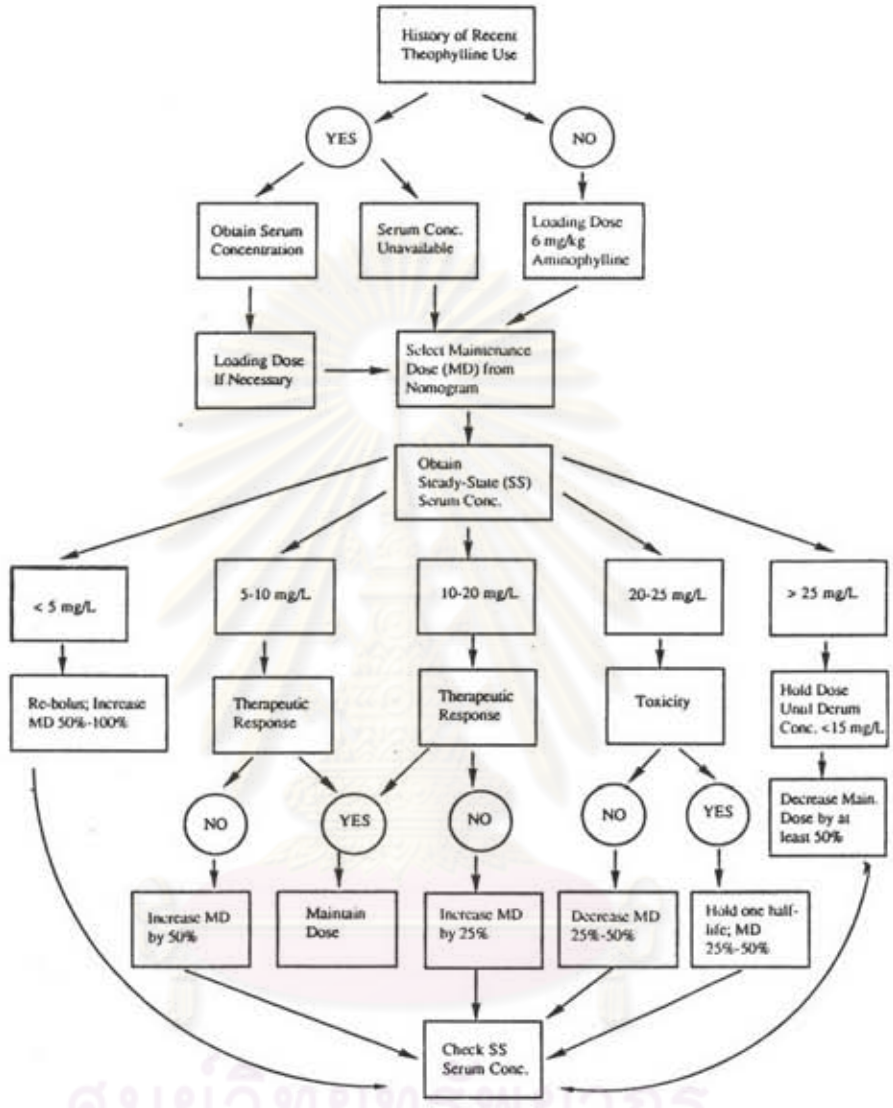

Figure 3 : Algorithm for theophylline dosing in the adult patient with acute bronchospasm. Suggested actions for particular serum concentrations should not be misconstrued as absolute. Factors such as compliance, assay accuracy, non-attainment of steady state and the response of the individual patient can complicate interpretation and may require an alternative course of action.

6. Therapeutic Monitoring of Theophylline

6.1 Therapeutic and Toxic Serum Concentrations

The usually accepted therapeutic range of 10 to 20 mcg/ml is not an absolute but a statistical concept. A range of 5 to 15 mcg/ml may well be as effective and a safe range of steady - state concentrations for most patients (Kelly and Hill, 1993). Most COPD patients were elderly and often have a rapidly changing clinical picture that can affect theophylline clearance. A range 10 to 15 mcg/ml would minimize the likelihood of toxicity (Stratton,1993). The improvement in respiratory function can be observed with plasma concentration as low as 5 mcg/ml (Bennett, et al., 1994; Bierman and Williams, 1989: Winter, 1992). Some patients may benefit from plasma theophylline levels of 20 mcg/ml or higher (Gibaldi, 1991). Neville and McDevitt (1991) reported that theophylline exerted a beneficial effect on lung function over the serum range 3 to 25 mcg/ml, the recommended therapeutic range is 10 - 20 mcg/ml. Hendeles et al. (1992) reported that from multicenter study conducted under the auspices of the American Academy of Allergy and Immunology, theophylline doses that often resulted in serum concentrations less than 10 mcg/ml provided nearly as much effect as an inhaled corticosteroid, beclomethasone diproprionate, in controlling chronic asthma.

Nausea and vomiting are the most common side effects of theophylline. These effects can occur at concentrations as low as 13 to 15 mcg/ml, they are observed more frequently at plasma concentration exceeding 20 mcg/ml. Seizures usually occur at plasma concentrations exceeding 50 mcg/ml (Winter, 1992). But seizures and atrial tachyarrhythmia have been reported with serum concentrations of 20 to 30 cmg/ml (Stratton, 1993). Tachycardia and hematemesis may occur at plasma concentration exceeding 15 mcg/ml (Benett et al., 1994). Some patients may experience nausea despite having drug concentration at the lower end of the therapeutic range (Frew and Holgate, 1993).

6.2 Blood Sampling Times for Theophylline Serum Assay

It is important that blood samples for measuring serum concentration during long term maintenance therapy be obtained when steady - state conditions are present (Hendeles, Iafrate and Weinberger, 1984). In most clinical situations, steady - state conditions can be assumed after three or four half - lives (Winter, 1993). Blood sampling in relation to administration of last dose (Bennett, 1994; Blackbourn and Sunderland, 1987)

Peak serum concentrations :

(a) plain tablets or solutions : 1 -2 hr post dose

(b) sustained release preparations (depending on the release characteristics of preparations

(1) one - daily preparations

: 8 - 12 hrs post dose

(2) twice - daily preparations

: 4 - 6 hrs post dose

Trough serum concentrations : immediately before the next dose

When Theo - Dur^{R} is used, the peak concentration will most often occur in adults at approximately 6 hours after the dose, however, considerable variability exists (Edwards et al., 1992). Manufacturers for once - daily theophylline preparations suggest that a serum sample should be obtained 12 hours after a dose for Theo - 24^{R} when determining the peak theophylline serum concentration (Kelly, 1993; Rogers et al., 1987). In patients receiving sustained - release theophylline products, the time of sampling is less critical. While trough concentrations are commended, samples obtained at the midpoint of the dosing interval may also be acceptable (Winter, 1992). The midpoint of dosing interval is a reasonable approximation to the time at which the Cpss ave (average serum concentration at steady state) occurs (Peck, Conner and Murphy; 1991). Both the efficacy and toxicity of theophylline correlate better with theophylline peak, rather than trough serum concentrations particularly with the substained release products (Kelly, 1993). Some authorities measure only the trough concentration; however, this is inappropriate in children or adults who are rapid metabolizers, since the peak concentration may be more than twice that of the trough. Before serum concentrations are determined during long-term therapy, the patients should have taken the drug as prescribed with no missed or added doses for at least 48 hours (Bennett et al., 1994).

6.3 Specimen Storage

Blood should be collected with sterile technique in red - top tubes. The blood should be centrifuged promptly and the serum separated. Although plasma may be used for analysis, serum is preferred. Samples not analyzed immediately should be stored frozen at - 20° c (Ellis and Hendeles, 1986). Bonham et al. (1980) suggested that theophylline remained in serum at room temparature for at least seven days, under refrigeration for at least 14 days, and when frozen for at least four months.

6.4 Assay Methods

The techniques available for measurment of serum theophylline concentration include spectrophotometric technique, radioimmunoassay (RIA) technique, gas liquid chromatographic technique, high - pressure liquid chromatographic (HPLC) technique, homogenous enzyme - multiplied immunoassay technique (EMIT^{R} , Syva, Palo Alto, CA), Fluorescence polarization immunoassy technique (Abbott TDX^{R}, Abbott Laboratories, North Chicago , IL), and combination immunoassay and thin layer chromatographic technique " Acculever " (System Medical Diagnostic, Palo Alto, CA) (Barnhart et al., 1988; Bierman and Williams, 1989).

Fluorescence Polarization Immunoassay (FPIA) and TDX^{R} Analyzer System (Abbott, TDX Training; Jolley, Stroupe, Schwenzer et al., 1981)

The Abbott TDX^{R} system is based on FPIA technique. This method combines competitive protein binding with fluorescence polarization to give a direct measurement without the need for a separation procedure. All competitive binding immunoassays for measuring therapeutic drugs are based on competition between the drug in the patient sample and a labeled drug, called tracer. Sample drug and tracer compete for a limited number of binding sites on antibodies specific to the drug being measured. The concentration of unlabeled drug from a patient sample will determine how much labeled drug can bind to the specific antibody. In the TDX^{R} system, the label on the tracer drug is the fluorescent dye - fluorescein. The changes of the polarization angle reflect tracer binding to antibody. The precise relationship between polarization and concentration of the unlabeled drug is established by measuring the polarization valves of calibrators with known concentrations of the drug. A calibration curve stored in system memory is used to automatically determine the concentrations of unkonwn patient samples.

Wilson et al. (1988) reported that TDX^{R} system offer acceptable sensitivity, accuracy, and precision when compared to the HPLC methods. Oles (1990) reported that advantage of this system include the ability to use whole blood (e.g., fingerstick samples), or plasma; limited machine start - up time; no required sample preparation; and a noncritical pipetting step.