CHAPTER 2

LITERATURE REVIEW

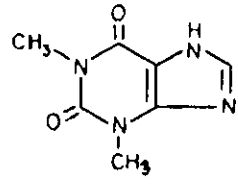
1. Theophylline

Theophylline was first introduced for the treatment of asthma in 1900, but its use did not become widespread until after 1936. Over the years, it has gained an increasing role in the management of patients with bronchospasm, and it is regarded by many physicians as the drug of choice in therapy for acute exacerbation of asthma (Bukowskyj., et al. 1984).

1.1 Chemistry

Theophylline (1,3–dimethylxanthine) is a naturally occurring alkaloid, structurally related to caffeine and theobromine (Joseph and Bertino, 1998). It occurs as a white, odorless, crystalline with a bitter taste (Labeling Guidance,1995). Pharmaceutically, theophylline is poorly soluble in water (8 mg/ml at 25°c solubility) (Joseph and Bertino, 1998). Anhydrous theophylline has the chemical name of 3, 7-dihydro-1, 3-dimethyl-1H-Purine-2, 6-dione, and is represented by the following structural formula: (Labeling Guidance, 1995; AHFS Drug Information, 1999). The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17.

Figure 1 Structure of theophylline anhydrous



1.2 Mechanism of action

Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels (Clinical pharmacology, 1996). It exhibits various

pharmacological actions in humans. There have been a number of cellular mechanisms of action as follows:

(1) Translocation of intracellular calcium,

(2) Inhibition of phosphodiesterase with the resultant accumulation of the cyclic nucleotide adenosine monophosphate (cAMP),

(3) Potentiation of prostaglandin synthesis and reduction of uptake or metabolism of catecholamines, and

(4) Blockade of adenosine receptors by acting as a competitive antagonist on both types of adenosine receptors.

Physiologically, theophylline can be categorized as affecting a number of various organ systems. For instances: (1) Central nervous system (2) CVS (3) Kidneys (4) GI tract (5) Lungs, and (6) Miscellaneous effects (Joseph and Bertino, 1998).

1.3 Pharmacokinetics and Pharmacodynamics

Despite the fact that pharmacokinetics of theophylline have been extensively studied, numerous studies continue to be published (Joseph and Berttno, 1998). Average theophylline pharmacokinetic parameters in various populations have been showed in Table 1.

Table 1 Average theophylline pharmacokinetic parameters in various populations

Population	Volume of Distribution (L/kg.)	Total body Cl (mL/min/kg)
Neonates[a]	0.69 ± 0.95	0.29 – 0.8
Children		
1 – 9 y	0.3 - 0.7[b]	1.15
9 – 12 y	0.3 - 0.7[b]	1.15
Adolescents (12–16 y)	0.3 - 0.7[b]	0.9
Adults		
Smokers	0.3 - 0.7[b]	1.2
Nonsmokers	0.3 - 0.7[b]	0.9
CHF,		
Cor pulmonale	0.48 - 1	0.36
Cirrhosis	0.45 - 0.64	0.36

[a]Cl depends on gestational age. Degree of hepatic function maturation and postbirth age

[b]Average 0.45 L/kg.

1.3.1 Absorption

Theophylline is generally well absorbed after oral administration. Conventional tablets produce peak serum concentrations within 60 minutes after administration. Liquids and suspensions are absorbed more rapidly.

Sustained–release preparations vary in the rate of absorption. Food can delay the rate, but not the extent, of absorption of some sustained–release products. Large volumes of fluid can increase absorption (Clinical Pharmacology, 1996). Another factor that has been shown to affect sustained–release theophylline absorption is circardian rhythm. Day–night differences exist in absorption, which higher peak concentrations and faster time to peak concentration being seen with morning dosing as opposed to evening dosing (Joseph and Bertino, 1998).

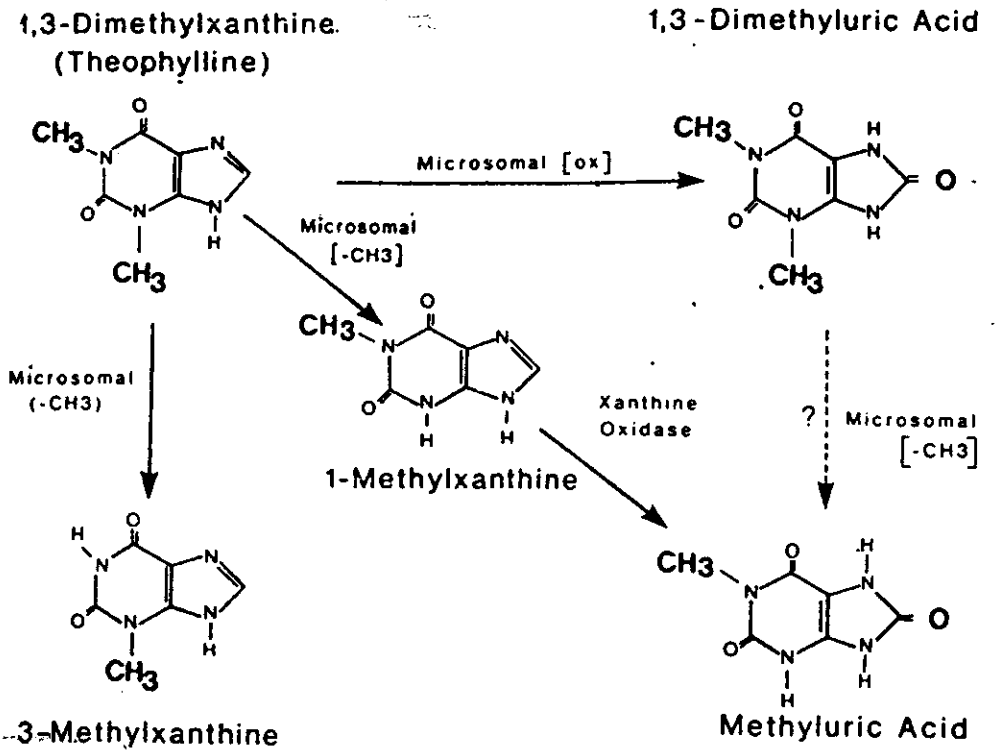
1.3.2 Distribution

Approximately 40% of theophylline are protein bound. Following an IV dose, distribution is complete within 60 minutes. Theophylline distributes into body water (Joseph and Bertino, 1998) followed by a two–compartment model with a Vd in adult ranging from 0.3 to 0.7 L/kg (Winter, 1988). In children the Vd also approaches 0.45 L/kg (Joseph and Bertino, 1998), whereas In premature newborns is approximately 0.7 L/kg (Winter, 1988).

1.3.3 Metabolism

Following oral dosing, theophylline does not undergo measurable first-pass elimination. In adults and children beyond one year of age, approximately 90% of dose are metabolized in the liver (Labeling Guidance, 1995). Theophylline biotransformation is mediated by the liver mixed-function oxidases, most likely the cytochrome P-448 system. (Bukowskyj., et al. 1984). In premature neonate, theophylline is metabolized to caffeine in significant amounts, and this compound can accumulate due to its long half–life. Theophylline elimination usually is a first-order process, but zero-order elimination had been reported in some cases. Theophylline's half-life varies with patient age, hepatic function, smoking status, and drug interactions. Nonsmoking adults usually have a half-life of 6.5-10.5 hours. For smokers and children age 1-9 ys, the half-life can be as short as 4-5 hours. Cor pulmonale, pulmonary edema, and cirrhosis can prolong the half-life to as long as 24 hours (Clinical Pharmacology, 1996), The average theophylline Cl is 0.04 L/hr/kg, based on lean or ideal body weight. (Winter, 1988). The Cl of theophylline varies widely among person and is altered by many factors (Maria., et al. 1984). A number of clinical factors will influence theophylline Cl such as smoking, diseases, diet, and drug interactions (Brown and lee, 1982; Winter, 1988).

Figure 2 Biotransformation of theophylline



1.3.4 Excretion

In neonates, approximately 50% of the theophylline dose are excreted unchanged in urine. Beyond the first three months of life, approximately 10% of the theophylline dose are excreted unchanged in the urine. (Jonkman and Upton, 1984) The remainder is excreted in the urine mainly as 1,3-dimethyuric acid (35-40%), 1-methyuric acid (20-25%) and 3-methyxanthine (15-20%). Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children > 3 months of age. In contrast, the large fraction of the theophylline dose excreted in the urine as unchanged form and caffeine. In neonates with reduced renal function, careful attention to dose reduction and frequent monitoring of serum theophylline concentrations is required (Labeling guidance, 1995).

1.4 Dosages

Dosages of theophylline must be individualized. Initial dosage should be based on lean body weight and dosage adjustments should be based on serum theophylline concentrations (Clinical pharmacology, 1996; AHFS, 1999).

Oral or IV dosage

- Adults 16-60 ys old and children > 45 kg: 300 mg/day PO/IV given in divided doses every 6-8 hours. After 3 days, if tolerated, increase doses to 400 mg/day PO/IV.

- Children 1-15 ys old and < 45 kg: 12-14 mg/kg/day PO/IV up to maximum of 300 mg/day, given in divided doses every 4-6 hours.

- Full term infants and infants up to 52 weeks old: Calculated initial doses based on the following: total daily dose (mg) = [(0.2 * age in weeks) + 5] * (kg body weight). In infants up to 26 weeks old, divide dose into 3 equal amounts and administer PO/IV at 8 - hours intervals and infants > 26 weeks old, administer in 4 equal amounts PO/IV at 6 - hours intervals.

Dosage titration should be done in patients with high risk factors for impaired for theophylline Cl, the elderly and those in whom monitoring theohylline concentrations are not feasible (Clinical Pharmacology, 1996).

IV infusion rate

Aminophylline: Rate of IV infusion should not exceed 7.5 mg/kg over 30 minutes. Because of the potential danger of a push dose, a convenient and practical approach to IV intermittent therapy is the dilution of the dose in approximately 50 ml of fluid followed by infusion over 30 minutes. However, intermittent therapy is less effective than a continuous IV infusion (Micromedex, 2000).

1.4.1 Design of dosage regimens (Shargel and Yu, 1999)

Several methods may be used to design a dosage regimen. Generally, the initial dosage of the drug is estimated using average population pharmacokinetic parameters as obtained from the literature. The patient is then monitored for the therapeutic response by physical diagnosis and, if necessary by measurement of serum drug levels. After evaluation of the patient, a readjustment of the dosage regimen may be indicated, with further TDM.

1.4.1.1 Individualized Dosage Regimens

The most accurate approach to dosage regimen design would be the calculation of the dose based on the pharmacokinetics of the drug in the patient. The readjustment of the dose may be calculated using pharmacokinetic parameters derived from measurement of the serum drug levels from the patient after the initial dose. Most dosing programs record the patient's age and weight and calculate the individual dose based on creatinine Cl and lean body weight.

1.4.1.2 Dosage Regimens Based on Population Averages

The method most often used to calculate a dosage regimen is based on average pharmacokinetic parameters obtained from clinical studies published in literature. This method may be based on a fixed or adaptive model.

1.4.1.3 Dosage Regimens Based on Partial Pharmacokinetic Parameters

For many drugs, the entire pharmacokinetics profile for the drug is unknown or unavailable. Therefore, the pharmacokineticist needs to make some assumptions to calculate the dosage regimen. Population pharmacokinetics uses average patient population characteristics and only a few SDCs from the patient. Its approach to TDM has increased with the increased availability of computerized databases and the development of statistical tools for the analysis of observational data.

1.4.1.4 Empirical Dosage Regimens

The physician characterizes the patient as representative of a similar well-studied clinical population that has used the drug successfully.

1.4.2 Dose adjustment by serum theophylline level

Obtain a peak serum level 2 hours after rapid - release formulations or 4 hours after slow - release products (Hendeles & Weinberger, 1983).

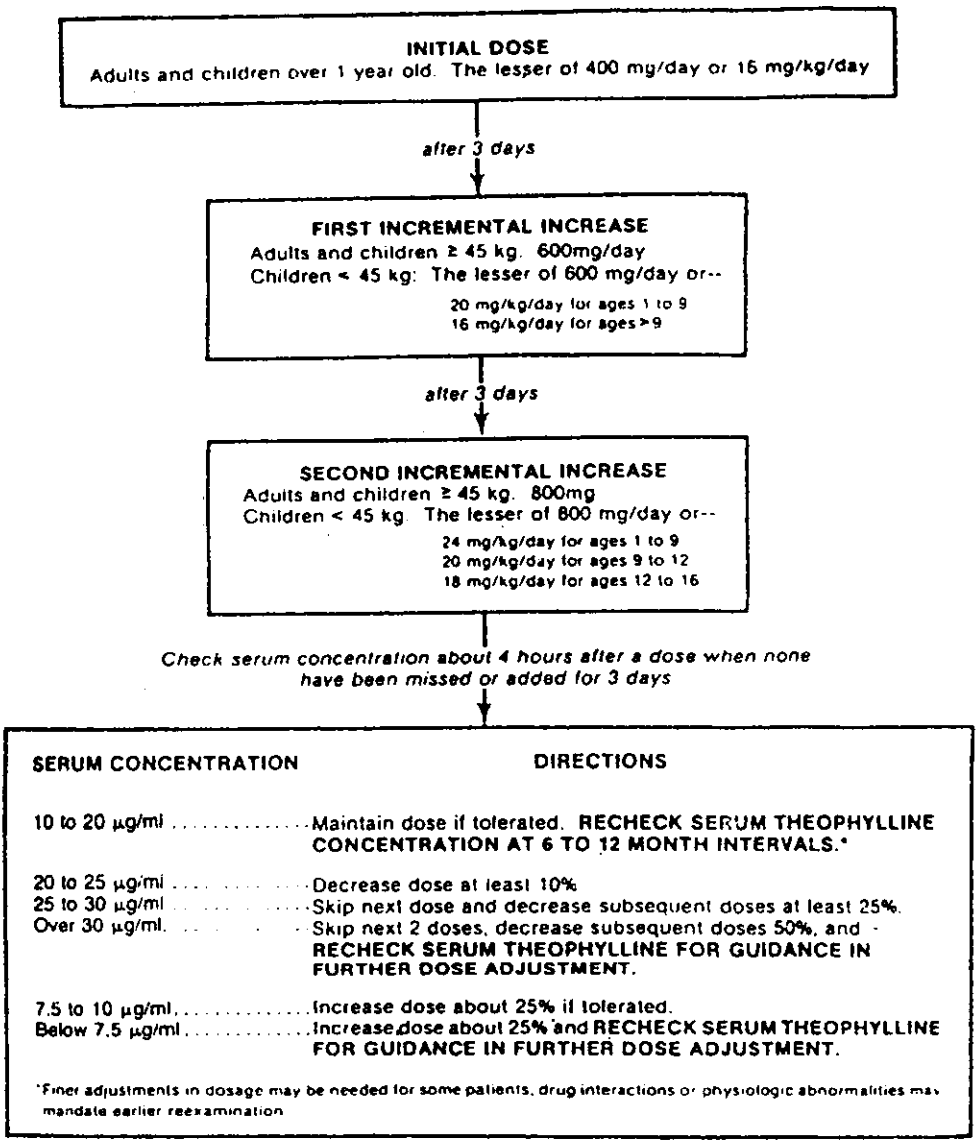
Table 2 Dose adjustment after serum theophylline measurement by Hendeles., et al (Drugdex, 1999)

Serum level	Dose adjustment
Less than 9.9	Increase dose 25 % and recheck level after 3 days
10 –14.9	Maintain dose if symptoms are controlled ; recheck serum levels at 6 to 12 month intervals ; if symptoms not well controlled and present dose tolerated, additional medication (s) should be considered
15 – 19.	10% decrease in dosage should be considered, even if current dosage is tolerated, to provide greater margin of safety
20 – 24.9	25% decrease in dose even if no adverse effects are noted; recheck serum level after 3 days
25 – 30	Skip next dose ; decrease subsequent doses 25% ; recheck level after 3 days
Greater than 30	Treat overdosage as indicated; if theophylline is resumed, dosage should be decreased 50%, recheck serum level after 3 days

Table 3 Dose adjustment after serum theophylline measurement by Joseph and Bertino (Joseph and Bertino, 1998)

Measured Serum Concentration (mcg/mL)	Dose adjustment
5–7.5	Increase dose 25%; recheck serum concentration in 3 d
7.5-10	Increase dose 25% only if patient is symptomatic ; recheck serum concentration in 3 d and every 6-12 months.
10-20	No change : consider decreasing dosage if >15 mcg/ml
20-25	Decrease dose by 10-25%; recheck in 3 d and every 6-12 months
25-30	Hold one dose ; decrease maintenance dose by 25% ; Recheck in 3 d and every 6-12 months
>30	Hold two doses ; decrease maintenance dose by 50%; recheck to guide dosage adjustment ; consider activated charcoal treatment for toxicity

Figure 3 Dose adjustment by FDA-approved package insert



Scheme for Establishing Optimal Oral Theophylline Dosage in Ambulatory Patients.
This is a conservative application of the recommendations incorporated into the FDA-approved package insert. Ideal body weight should be used for obese patients. Dose recommendations are unique for infants under one year of age; the clinician should review the recommendations of Nassif et al. before treating patients in this age group.

The necessity to individualize theophylline dosage over a wide range is well documented. Several studies have shown that usual doses of 400-800 mg of theophylline per day are often less than optimal during chronic administration in some patients and toxic in others. Since the cumulative frequency distribution for therapeutic and toxic concentrations overlap, no dose or dose range can guarantee both efficacy and safety (Hendeles., et al. 1995; Drugdex, 1999).

Correlation between Dose and Plasma Concentrations

The clinical use of theophylline is complicate with a poor correlation between dose and concentrations; empirical dosing regimens often do not lead to predictable serum concentrations of the drug. This predictability arises from a number of factors such as poor compliance, variation in bioavailability between preparations and inter-individual difference in drug metabolism, another factor may be nonlinear theophylline pharmacokinetics due to saturation of the drug-metabolizing enzymes. The significance of nonlinear pharmacokinetics is that a small increase in drug dose may lead to a disproportionately large rise in serum concentrations (Skinner M.H., 1990).

1.5 Factor affecting theophylline elimination

It has been reported that the Cl of theophylline can be affected by many factors such as age, diet, smoking habits, complicating diseases and other drug concurrently being taken (Yano I., et al. 1993; Tanigaware Y., et al, 1995). The details of these factors are as follows:

1.5.1 Age

Clearance of theophylline has been shown to vary with age. It is reduced in infants and elderly patients. Children up to adolescence have rapid Cls. (Bukowskyj., et al, 1984), In nonsmoking adults with normal liver and cardiac function, theophylline average half-life is 5-6 hours. Delayed elimination is observed in very young and older patients (above 50 ys). Neonates have a half-life of approximately 30 hours (Brown and Lee, 1982; William., et al.1984).

1.5.2 Heart disease

Patients on theophylline therapy may develop CHF either left or right sided. Acute pulmonary edema has been reported to cause marked decreases in theophylline Cl, although mild CHF may not affect Cl. Cor pulmonale in the presence of chronic obstructive lung disease has also been reported to cause a decrease in theophylline Cl (Bukowskyj., et al, 1984). The presence of certain disease state and the degree of their control influence theophylline elimination. The patient's theophylline elimination become more prolonged as his/her disease worsens, but it may also shorten – or even return to normal as the disease is better controlled (Brown and Lee, 1982).

1.5.3 Liver disease

Theophylline Cl can be markedly depressed in the patients with hepatic disease, especially those with cirrhosis. The magnitude of the decrease in Cl varied with the type of dysfunction. The most marked decrease in Cl occurred in the patients with "decompensated cirrhosis". Acute hepatitis also caused a depression of Cl that was not as low as that in the patients with decompensated cirrhosis. Patients with cholestatis and compensated cirrhosis did not differ substantially from health controls (Bukowskyj., et al.1984). Patients with cirrhosis have greatly delayed excretion because of their decreased liver function and diminished ability to metabolize the drug (Brown and Lee, 1982). The inter-subject variability in the kinetic disposition of theophylline in cirrhotic patients is consistent with the variability in hepatocellular function observed in this disease. Patients with chronic hepatic cirrhosis have a variable capacity to eliminate theophylline that cannot readily be predicted from the usual laboratory test of hepatic function (Piafsky K M., et al. 1977.).

1.5.4 Tars from smoking and charcoal broiling

Cigarette smoking has consistently been correlated with high rates of theophylline Cl. A correlation has been reported between serum thiocyanate

concentrations in smokers and their theophylline Cls, suggesting that the greater the number of cigarettes smoked, the more rapid the Cl of theophylline (Bukowskyj., et al. 1984). Some suggest that this effects occurs when a person smokes more than 10 cigarettes per day or 1 to 2 marijuana cigarettes per day (Brown and Lee, 1982). Passive smokers defined as nonsmokers with long-term exposure to cigarette smoke metabolize theophylline more rapidly than nonsmokers (Matsunga., et al. 1989).

1.5.5 Infections

Infections caused a decreased in theophylline Cl. There were many reports referring to an alteration of theophylline Cl in the presence of infections. The controversy over alteration of theophylline metabolism by influenza vaccination may be explained by either differences in types of vaccine or differences in potencies of batches of vaccines. The precise relation, however, between infection or vaccination and theophylline metabolism remains ambiguous. (Bukowskyj., et al. 1984).

1.5.6 Cystic fibrosis

A recent report has described markedly increased Cl of theophylline in the patients with cystic fibrosis (Bukowskyj., et al. 1984).

1.5.7 Miscellaneous

Other factors associated with decreased theophylline Cl include the third trimester of pregnancy, sepsis with multiple organ failure, hypothyroidism (Vozeh SV., et al, 1984; Labeling guidance, 1995).

1.6 Indications

Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases e.g. emphysema and chronic bronchitis (Labeling Guidance, 1995; Clinical Pharmacology, 1996). Theophylline relieves the primary manifestations of asthma,

including shortness of breath, wheezing and dyspnea, and improves pulmonary function as measured by increased flow rates and vital capacity (AHFS, 1999).

Other uses

IV theophylline is used to relieve a number of symptom, including:

- periodic apnea and increase arterial blood pH in patients with cheyne-stokes respiration,
- adjunct in the treatment of pulmonary edema or paroxysmal noctural dyspnea caused by left-sided heart failure,
- augment the diuretic action of the thiazides and carbonic anhydrase inhibitors, and to relieve dyspnea, decrease venous filling pressure and increase cardiac output when used as an adjunct in the treatment of CHF (AHFS, 1999).

1.7 Adverse Drug Reactions

In addition to its multitude of pharmacological effects, theophylline can cause significant (and sometimes life-threatening) adverse effects. Two major categories of theophylline poisoning exist: the acute ingestion and chronic-use intoxication. Because of its complex hepatic elimination, chronic-use intoxication often occurs in the patient who can least tolerate the development of adverse effects, that is the patient with chronic liver, pulmonary or cardiac disease (Joseph and Bertino, 1998).

1.7.1 Non-life-threatening adverse effects include nausea, heartburn, diarrhea, and central nervous system stimulation, including irritability, insomnia, and tremor. These so-called minor side effects can occur at therapeutic and subtherapeutic concentrations and frequently have resulted in cessation of therapy (Bukowskyj., et al, 1984).

1.7.2 Life–threatening adverse effects associated with theophylline administration are seizures and cardiac arrhythmias. Seizures occur with increasing

frequency when serum theophylline concentrations are greater than 40 mg/ml. Seizures are particularly dangerous because they may occur without warning signs of toxicity and are often refractory to usual anticonvulsant therapy. Mortality associated with theophylline–induce seizures has been reported to be about 50% (Bukowskyj., et al. 1984).

Sign or symptom of theophylline toxicity (Gordon., et al. 1991).

1. Cardiovascular system

Arrhythmia, i.e., sinus tachycardia, premature ventricular contractions, supraventricular tachycardia, premature atrial contractions, and multifocal atrial fibrillation were reported (Gordon., et al. 1991). Tachycardia is commonly observed in theophylline over dose and with severe intoxication hypotension may occur (Skinner, 1991).

2. Gastrointestinal system

Theophylline may also increase acid secretion. Symptom relating to the GI system are the most common adverse effects observe with theophylline (Skinner, 1991). These symptoms were nausea, vomiting and diarrhea (Gordon., et al, 1991).

3. Central nervous system

Seizure is the most serious complication of theophylline toxicity. Serum theophylline concentrations are a poor predictor of seizure. Seizures are most commonly observed in the patients with serum concentrations of more than 40 to 50 mg/L (Skinner, 1991). Other central nervous symptom such as agitation, tremor, altered behavior, headache (Gordon., et al. 1991).

4. Others (Gordon., et al. 1991)

4.1 Severe hypokalemia

4.2 Acute psychosis

4.3 Dysphagia

4.4 Acute urinary retention

4.5 Acute renal failure

4.6 Right upper quardrant pain stimulating biliary colic

A range of clinical signs and symptom may manifest theophylline toxicity. Mild toxicity may produce tachycardia, nausea and vomiting, wakefulness and respiratory alkalosis. Palpitation, tremor, headache and abdominal pain suggest moderate intoxication. In severe intoxication there may be hypotension, cardiac arrhythmia, altered conscious, seizures and profound metabolic and electrolyte disturbance. Unfortunately, signs of severe intoxication may not be predicted by any of the signs of mild toxicity, such as nausea (Skinner, 1990).

Adverse effects associated with route and method of administration.

Rapid IV injection of aminophylline may produce dizziness, fatigue and light headaches, palpitation, syncope, precordial pain, flushing, premature bradycardia, premature ventricular contractions, severe hypotension or cardiac arrest. IM injection of aminophylline produces intense local pain; IM dyphylline reportedly produces little tissue irritation when administered rectally as suppositories, theophylline cause rectal irritation and inflammation (AHFS Drug Information, 1999).

Correlation between serum concentration and toxicity

Adverse reactions are not readily predictable from the drug concentration alone (Skinner, 1990). At blood levels of less than 20 mcg/ml, or slightly above, the most frequent adverse effects involve the GI system and the central nervous system, although a small percentage of these adverse effects may occur within the therapeutic range. At concentrations of 20 mcg/ml to 40 mcg/ml and greater, cardiac effect are seen. Levels of 40 mcg/ml and greater have been associated with focal or generalized seizures, may also occur at lower concentrations (Brown and Lee, 1982; Skinner, 1990).

Treatment of theophylline toxicity

The first and most important step in the treatment of toxicity is to stop the drug immediately. To verify the treatment of suspected toxicity, a serum sample should be obtained for theophylline analysis at once. Without the continued

administration of theophylline, drug elimination by the body will naturally return the levels to within the therapeutic range (Brown and Lee, 1982).

- Treatment of seizures

Because of the high morbidity and mortality associated with theophylline-induced seizures, treatment should be rapid and aggressive. Anticonvulsant therapy should be initiated with an IV diazepam in increment of 0.1-0.2 mg/kg every 1-3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital 20 mg/kg infused over 30-60 minutes (Skinner, 1991; Labeling Guidance, 1995).

- Treatment of cardiac arrhythmias

Sinus tachycardia and simple ventricular premature beats are not harbingers of life-threatening arrhythmias, they do not require treatment and they resolve with declining serum theophylline concentrations. Other arrhythmias, especially those associated with hemodynamic compromise, should be treated with antiarrhythmic therapy appropriate for the type of arrhythmias (Bukowskyj., et al. 1984; Labeling Guidance, 1995).

- Gastrointestinal decontamination

Oral activated charcoal 0.5 g/kg up to 20 g and repeat at least once 1-2 hours after the first dose is extremely effective in blocking the absorption of theophylline throughout the GI tract, even when administered several hours after ingestion (Labeling Guidance, 1995).

1.8 Contraindication / Precautions

Theophylline is contraindicated in the patients with a history of hypersensitivity to theophylline or other in the product (Labeling Guidance, 1995). and precautions should be taken in these patients with acidemia, peptic ulcer, hyperthyroidism, glaucoma, diabetes mellitus, severe hypoxemia, cardiac disease, heart failure, cholestasis, cor pulmonale, pulmonary edema, seizure disorder, hepatic disease, fever, and sepsis (Clinical pharmacology, 1996; AHFS, 1999).

Pregnancy

Category C: There are no adequate and well control studies in pregnant women. Although safe use of theophylline during pregnancy has not been established relative to the potential risk to the fetus, the drugs have been used during pregnancy without teratogenicity or other adverse fetal effect. Their safety during pregnancy clearly needed is generally not seriously questioned (Labeling Guidance, 1995; AHFS, 1999).

Nursing Mothers:

Theophylline is excreted into breast milk and may cause irritability or other signs of mild toxicity in nursing human infants. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations (Labeling Guidance, 1995). The risk to the breast-fed infant must be weighed against the benefit of nursing in lactating women who are receiving theophylline (AHFS, 1999).

1.9 Drug Interactions

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamics, i.e., alterations in the therapeutic response to theophylline or another drug or occurrence of adverse effects without a change in serum theophylline concentrations. More frequently, however, the interaction is pharmacokinetics, i.e, the rate of theophylline Cl is altered by another drug resulting in increased or decreased serum theophylline concentrations (Jonkman and Upton, 1984; Upton, 1991; Loi., et al. 1991; Labeling Guidance, 1995; Tatro, 2000). Coadministration of more than 1 drug such as cimetidine with ciprofloxacin, causes a greater impairment of theophylline biotransformation than each inhibitor alone (Davis., et al.1992; Loi., et al.1993).

1.9.1 Pharmacokinetics Drug Interactions

- In Vitro Drug Interactions

The physical and chemical properties of theophylline present a problem for IV admixture because the drug precipitates in acid solutions. Theophylline was reported as being incompatible with ascorbic acid, penicillin potassium, tetracycline and vancomycin. Fortunately, multi-drug additions to IV infusions are now uncommon. The choice of solution for use as a vehicle for theophylline should depend upon the pH; the recommended solution is dextrose 5% in water (McElnay J.C., 1982).

- Drug Interaction in the Intestine

Certain factors, such as changes in gastric pH, altered motility of the GI tract, and the amount and consistency of food ingested at the same time as the drug, can affect drug absorption. Concomitant administration of antacids and adsorbents, as well as certain ionic interactions and malabsorption syndromes, can also influence drug absorption profiles (McElnay J.C., 1982).

- Interactions Involving Metabolizing Enzyme Systems.

Theophylline's elimination from the body involves biotransformation in the liver and urinary elimination as 1-3 dimethyuric acid, 1 methyluric acid, and 3 methylxanthine, with approximately 7-13% being excreted unchanged. The hepatic extraction ratio for theophylline in healthy subjects is approximately 10%. It appears that theophylline would be susceptible to drug interaction involving enzyme induction or inhibition, but would not be influenced significantly by changed rates of liver perfusion (McElnay J.C., 1982).

1.9.2 Pharmacodynamics Drug Interactions

Drug combinations are often used clinically to take advantage of interactions that affect the same receptor sites or physiological systems. Adjuvant therapy with other bronchodilators is often used in asthmatics.

- Interaction with other bronchodilators

β2-stimulant drugs increase cAMP production while theophylline inhibits its breakdown, giving rise to potential additive bronchodilator

effects such as ephedrine, metaproterenol, terbutaline, and albuterol (McElnay J.C., 1982).

Clinically significant drug interactions with theophylline (Reitberg., et al. 1981; Zarowitz, Szefler and Lasezkay, 1981; Bavman J.H. and Kimelblalt B.J., 1982; May D.C., et al. 1982; Reed and schwartz, 1983; Jonkman and Upton, 1984; Upton, 1991; Loi, Wei and Vestal, 1991; Loi C.M., Weix and Vestal R.E., 1991; Lee L.B., et al. 1991; Hurwitz A.H., et al. 1991; Davis., et al. 1992).

Drug	Type of interaction	Effect
Adenosine	Theophylline blocks adenosine receptors.	Higher doses of adenosine may be required to achieve desired effect.
Alcohol	A single large dose of alcohol (3 ml/kg. of whiskey) decreases theophylline Cl for up to 24 hours.	30 % increase
Allopurinol	Decrease theophylline Cl at allopurinol dose > 600 mg/day	25 %increase

Drug	Type of interaction	Effect
Aminoglutethimide	Increase theophylline Cl by inhibition of Microsomal enzyme activity.	25 %increase
Carbamazepine	Similar to Aminoglutethimide	30 % decrease
Cimetidine	Decrese theophylline Cl by inhibiting cytochrome P450 1A2	70 % increase
Diazepam	Benzodiazepines increase CNS concentrations of Adenosine, apotent CNS depressant, while theophylline blocks adenosine receptor	Larger Diazepam dose may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression
Disulfiram	Decrease theophylline Cl by inhibition hydroxylation and demethylation	50% increase
Enoxacin	Similar to cimetidine	300 % increase

Drug	Type of interaction	Effect
Erythromycin (erythromycin estolate, sterate not with erythromycin base)	Erythromycin metabolite decrease theophylline Cl by inhibiting cytochrome P450 3A3	35 % increase. Erytromycin steady state serum concentrations decrease by a similar amount
Estrogen	Estrogen containing oral contraceptive decreases theophylline Cl in dose-dependent fashion. The effect of progesterone on theophylline Cl is unknown	30 % increase
Flunazepam	Similar to diazepam	Similar to diazepam
Fluvoxamine	Similar to cimetidine	Similar to cimetidine
Halothane	Halothane sensitizers the myocardium to catecholamines, theophylline increase release of endogenous catecholamines.	Increase risk of ventricular arrhythmia
Interferon, human recombinant alpha-A	Decrease theophylline Cl	100% increase

Drug	Type of interaction	Effect
Isoprotrerenol (IV)	Increase theophylline Cl	20% decrease
Quinolone	Inhibition of the hepatic metabolism of theophylline	Increase theophylline levels with toxicity can occur
Ketamine	Pharmacologic	May lower theophylline seizure threshold
Lithium	Theophylline increase renal lithium Cl	Lithium dose required to achieve therapeutic serum increase an average of 60 %
Lorazepam	Similar to diazepam	80 % increase
Methothexate (MTX)	Decrease theophylline Cl	20 % increase after low dose MTX, higher dose MTX may have a greater effect
Mexilitine	Similar to disulfiram	80 % increase
Midazolam	Similar to diazepam	Similar to diazepam

Drug	Type of interaction	Effect
Pancuronium	Theophylline may antagonized non-depolarizing neuromuscular blocking effect; possibly due to phosphodiesterase inhibition	Large dose of pancuronium may required to achieve neuromuscular blockade
Pentoxifylline	Decrease theophylline Cl	30 % increase
Phenobarbital (PB)	Similar to aminogluthetimide	25 % decrease after two weeks of concurrent PB
Phenytoin	Phenytoin increases theophylline Cl by increasing microsomal enzyme activity. Theophylline decrease phenytoin absorption	Serum theophylline and phenytoin concentrations decrease about 40 %
Propafenone	Decrease theophylline Cl and pharmacologic interaction	40 % increase Beta-2 blocking effect may decrease efficacy of theophylline

Drug	Type of interaction	Effect
Rifampicin	Increase theophylline Cl by increasing demethylation and hydroxylation. Decrease renal Cl of theophylline.	20 % decrease
Sulfinpyrazone	Increase theophylline Cl by increasing demethylation and hydroxylation. Decrease renal Cl of theophylline	20 % decrease
Tacrine	Similar to cimetidine, also increase renal Cl of theophylline	90 % increase
Thiabendazone	Decrease theophylline Cl	190 % increase
Ticlopidine	Decrease theophylline Cl	60 % increase
Troleandomycin	Similar to erythromycin	33-100 % increase depending on troleandomycin dose

Drug	Type of interaction	Effect
Beta-blockers	Pharmacologic antagonism. Beta blocker may reduce The n-demethylation of theophylline	30-50 % increase
Caffeine	Interferance with theophylline metabolism	Serum theophylline concentration may be increased
Corticosteroids	Alteration in pharmacologic activity of theophylline	21 % increase
Famotidine	Increase theophylline concentrations	Possibly producing toxicity
Felodipine	Possibly decrease GI absorption of theophylline	Serum theophylline level may be decrease
Isoniazid	Isonizid may induce and inhibit the hepatic enzymes responsible for theophylline metabolism	Mild reduction and elevations in theophylline plasma levels have occured

Drug	Type of interaction	Effect
Propylthiouracyl	Increase theophylline Cl can be expected in hyperthyroid patients. Cl returns to normal when euthyroid state is achieved	Serum theophylline level may be decrease
Spiramycin	Spiramycin metabolite decrease theophylline Cl by inhibiting cytochrome P450	Serum theophylline level may be increase.

2. Therapeutic Monitoring of Theophylline

2.1 Monitoring theophylline therapy to prevent toxicity

The process for prevent theophylline toxicity is listed as follows:

- Education pharmacy and therapeutics (P&T) committee encourages clinicians to rethink the use of theophylline.

- Monitoring serum theophylline concentrations if the patient had symptom consistent with theophylline toxicity or had risk factors for toxicity.

- Screening orders for potential drug interactions and Laboratory monitoring (Anne., et al. 1996).

Serum theophylline concentration should be measured in cases as follows:

- When initiating therapy to guide final dosage adjustment after titration.

- Before making a dose increase to determine whether the serum concentration is in sub-therapeutic level for a patient who continues to be symptomatic.

- Whenever signs or symptoms of theophylline toxicity are present.

- Whenever there is a new illness, worsening of a chronic illness, or change in the patient treatment regimen that may alter theophylline Cl (Gordon., et al. 1991).

2.2 Blood sampling times for theophylline serum assay

It is important that blood samples for measuring serum concentrations during long term maintenance therapy be obtained when steady-states conditions are present. In most clinical situations, steady-state conditions can be assumed after three or four half-lives (Winter, 1988).

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) once – daily preparations

: 8 – 12 hrs post dose

(2) twice – daily preparations

: 4 – 6 hrs post dose

Trough serum concentrations: immediately before the next dose. In contrast, when signs or symptoms of theophylline toxicity are present, the serum sample should be obtained as soon as possible analyzed immediately and the result reported to the clinician without delay.

(Research and Development Laboratories, 1980; Labeling Guidance, 1995)

Interpretation of serum drug level

Correct ordering and interpretation of serum drug level also requires knowledge of the distribution and elimination characteristics of the drug. Serum

drug levels may only correlate with a therapeutic effect after the serum concentration has equilibrated with tissue concentrations (i.e., post-distributive phase). Thus, serum drug levels drawn during the distributive phase may yield no useful information. Serum drug levels also need to be assessed as to whether they are likely to represent a steady–state concentrations. Steady–state concentrations will generally be the most useful for adjusting the dosing rate of a drug. Serum drug levels ordered or interpreted without regard to the above principles may not only be useless but may lead to inappropriate therapeutic decisions
(D' Angio R.G., et al. 1990.).

3. Pharmacist's Role in Clinical Pharmacokinetics Monitoring

The following responsibilities should be part of clinical pharmacokinetics services or monitoring conducted by pharmacists (Am J Health-Syst Pharm, 1998).

3.1 Designing patient – specific drug dosage regimens based on the pharmacokinetics and pharmacological characteristics of the drug products used, the objective of drug therapy, and other pertinent patient factor (e.g., demographics, laboratory data) that improve the safety and effectiveness of drug therapy and promote positive patient outcomes.

3.2 Recommending or scheduling measurements of drug concentrations in biologic fluids or tissues in order to facilitate the evaluation of dosage regimens.

3.3 Monitoring and adjusting dosage regimens on the basis of pharmacological responses and biological fluid and tissue drug concentrations in conjunction with clinical signs and symptoms or other biochemical variables.

3.4 Evaluating unusual patient responses to drug therapy for possible pharmacokinetic and pharmacological explanations.

3.5 Communicating patient-specific drug therapy information to physicians,

nurses, and other clinical practitioners and to patients orally and in writing, and including documentation of this in the patient's health record.

3.6 Educating pharmacists, physicians, nurses, and other clinical practitioners about pharmacokinetic principles and appropriate indications for clinical pharmacokinetic monitoring, including the cost-effective use of drug concentration measurements.

3.7 Developing quality assurance programs for documenting improved patient outcomes and economic benefits resulting form clinical pharmacokinetic monitoring.

3.8 Promoting collaborative relationships with other individuals and departments involved in drug therapy monitoring to encourage the development and appropriate use of pharmacokinetic principles in pharmaceutical care.

4. Methods of Theophylline Dosing and Application of Pharmacokinetic Monitoring

4.1 Predictive algorithms

A number of predictive methods had been proposed as follows:

4.1.1 Dose-titration scheme by Weinberger & Hendeles, 1983 for determining maintenance requirements for oral theophylline and the stability of steady- state serum concentrations in compliant patients. In general, the dose-titration scheme resulted in the attainment and maintenance of serum concentrations in the target range for the majority of patients (Milavetz., et al. 1986).

4.1.2 Nomogram based on a single–point maintenance dose prediction method by slattery, 1980. A single serum theophylline determination was taken to predict the maintenance dosage required to achieved a target steady-state concentration of 12 mg/L. A single-point method is reliable and convenient in

achieving therapeutic theophylline concentrations in non smoking patients, but the use of this method in cigarette smokers results in underestimation of dosage requirements (Wilkend., et al. 1984).

4.1.3 'condition correction factor' method of estimating theophylline Cl by Powell., et al. 1978. A standard Cl of 40.9 ml/hr/kg bodyweight and condition correction factors of 1.57 for smokers, 0.43 for patients with CHF, 0.37 for those with pneumonia, and 0.84 for those with severe bronchial obstruction were used. If more than one 'condition' was present in the same patient, the factors were multiplied. No significant (p-value of 0.05) correlation were observed between actual and estimated theophylline Cl values. A lowering in the predictability of theophylline Cl as the number of correction factors increased was observed. The author hypothesized that the condition correction factor method may be useful in the patients with multiple conditions where close monitoring of serum concentrations is essential (Haumschill and Murphy, 1985).

4.2 Pharmacokinetic–Based Dosing Methods

4.2.1 The method described by Chiou., et al. Jonson and Burkle found that the Chiou method can be used to predict steady-state theophylline concentrations rapidly and accurately from only 3 blood samples, and that it may also be useful in patients with factors that influence theophylline disposition. Laaban., et al. confirmed that the Chiou method may be useful as a guide to provide early estimation of theophylline dosage but further serum concentrations determination is warranted to ensure that adequate concentrations have been achieved (Laaban., et al.1986). Pancorbo used computer simulations to evaluate the theoretical predictability of the Chiou and Koup., et al methods in estimating the total body Cl of theophylline, and assessed the effects of variation in Vd on that predictability. The predictability of the 2 methods differed considerably (Pancorbo, 1986). The Chiou technique

was selected as a representative example of the pharmacokinetic approaches to individualized dosing (Jenny R.W., 1991).

4.2.2 Otero., et al. validated the theophylline Cl estimated by patient population pharmacokinetics (method A), and compared with those obtained by applying the standard bibliographic mean values for Cl from Powell., et al.(method B). It was found, for patients without interfering indicator factors and patients with CHF, that the theophylline Cl values from method A produced predictions of the STC significantly less biased than those from method B. However, there were no differences between the methods as regards to accuracy for the group of smokers and when all patients were considered globally. Both methods showed an overall tendency to over-predicted STC, which reflects an underestimation of the Cl. The performance of both methods in term of precision reveals no statistically significant difference (Otero M.J., 1996).

Melethil S., Carlson J.D. and Havg M.T. used the nomogram to predict theophylline level in each patient and the patient was assigned as group 1, 2 or 3 based on clinical criteria stated in the nomogram. The patients younger than 50 ys, without liver disease nor CHF, were classified as group 1. Those patients 50 ys or older and either without liver disease or CHF belonged to group 2 and group 3 patients had either CHF or liver disease. The results indicate that the pharmacokinetic values assigned to groups 2 and 3 are good estimates of their true values. Since a myriad of factors influence theophylline Cl rates, the pharmacokinetic parameters derived from the nomogram and literature may not be applicable to all elderly (group 2) patients or those with CHF or liver disease (group 3). Therefore, it may become necessary to adjust initial dosage regimens based on plasma theophylline concentrations to ensure therapeutic efficacy and to prevent drug-induced toxicity (Melethil S., Carlson J.D. and Haug M.T.,1982).

4.3 Bayesian Parameter Estimation

Bayesian parameter estimation has been most frequently used for drugs with narrow therapeutic ranges. The concept of Bayesian parameter estimation was introduced into TDM in the 1970s. Sheiner, et al. 1979 presented its theoretical framework and this was followed by a number of microcomputer implementation and validation studies. In the past 10 ys or so, the technique has found a very useful place in TDM, particularly where drug concentrations are measured during relatively complicated dosage regimens, not at steady – state, and where only very few (1 or 2) concentration measurements are permissible. In these circumstances, it may be highly desirable to estimate pharmacokinetic parameter – principally clearance(Cl) and Volume distribution (Vd) in an individual patient so that drugs dosages can be adjusted to achieve specific target concentrations. The population pharmacokinetic parameters can be most readily estimated using specific software designed to handle such data, for example, the NONMEM® program. In this respect, the data set should consist of a sufficient number of patients to characterize the pharmacokinetic variability that exists in the population. In general, when compared with other method the Bayesian program was superior to dosage algorithms in the calculation of dosage and was as good as or better than other methods in the estimation of Cl or prediction of future concentrations (Thomson A.H. and Whiting B., 1992). Prediction by the Bayesian approach is slightly superior to other forecasting methods (Desoky E.E., et al. 1993).

A computerized method of pharmacokinetics interpretation of a single serum theophylline concentrations. Revise predictions of the profiles were generated by Bayesian analysis using a single serum theophylline concentrations taken during a previous out patient appointment. Comparing the predicted and measured profiles, the accuracy of the Bayesian method is considered more than adequate for clinical purposes. The predictions produced by the revised estimates were statistically less biased and more precise than those derived by a theophylline algorithm using population data (Chrystyn H., et al. 1989). Practitioners can be

more effective in their use of serum drug concentration data. This approach should result in better decisions about patient status, reduce the number of unnecessary drug concentrations and decrease the cost of TDM (Schumacher G.E. and Barr J.T., 1994). Revised predictions of the profiles were generated by Bayesian analysis using a single serum theophylline concentration taken during a previous outpatient appointment comparing the predicted and measured profiles. The accuracy of the Bayesian method is considered more than adequate for clinical purposes. The predictions produced by the revised estimates were statistically less biased and more precise than those derived by a theophylline algorithm using population data. The dosage recommendations made should allow an optimal compromise between the maximal clinical effect and minimal toxicity to be achieved (Chrystyn H.C., et al.1989). Murphy, et al. evaluated of Bayesian Microcomputer predictions of theophylline concentrations found that computer program predictions based on one measured feedback concentration were more accurate and precise than population-based predictions. Refinement of population parameters or two feedback concentrations further improved performance. Bayesian algorithm may make achieving therapeutic concentrations easier, quicker, and more precise (Murphy M.G., et al. 1990; Thomson A.H. and Whiting B., 1992).

4.4 Prediction of theophylline dosage regimens from two serum sampling

Two serum theophylline samples timed appropriately with the IV administration of aminophylline can project dosage regimens for individual patients. The measurement of two well-spaced serum theophylline levels as a basis for dosage adjustments appears to be a more individual approach than nomograms to the problem of designing appropriate theophylline dosage regimens (Robinson J.D., et al. 1982).

5. Prevention for Theophylline Toxicity

5.1 Monitoring serum theophylline concentrations was recommended for the following cases: (Lubischer A.V. and Lucas L.M., 1996).

5.1.1 The patients who had symptoms consistent with theophylline toxicity

5.1.2 The patients who had risk factors for toxicity, which included the addition of interacting medications, changes in the patient's condition that could alter theophylline Cl.

5.1.3 The patients who get or increase in dosage to > 400 mg/day

5.1.4 The patients who get new formulary product.

5.2 Screening orders for potential drug interactions. Had drug interactions occured, pharmacist should contact the prescriber to discuss for the appropriate dose (Lubischer A.V. and Lucas L.M., 1996).

5.3 Management errors contributing to theophylline toxicity (Gordon., et al 1991).

5.3.1 Delay (> 10 hours) from time toxic level was drawn to action by physician

5.3.2 Inappropriately high doses administered to patient with congestive heart failure or liver disease

5.3.3 Failure to note obvious (GI, cardiac, central nervous system) symptoms or signs of toxicity.

5.3.4 Recurrent toxicity with failure to be aware of, or to adjust dose

5.3.5 Dosing confusions and errors for patients without CHF

5.3.6 Emergency department IV treatment despite pretreatment levels ultimately found > 20 mcg/ml

5.3.7 Inadvertent overlap of IV aminophylline and oral theophylline

5.3.8 Interacting drugs ; failure to adjust dose or closely monitor

5.3.9 Patient discharged on same dose despite toxicity

5.3.10 Patient discharged with no noted physician awareness of toxicity.

Corrective Measures Implemented

Problem	Corrrective actions
1. Delay from time toxic level was draw to physician action	-Redesign of reporting system, including protocol for reporting if ordering physician not reached or off duty -Laboratory-based surviellance by clinical pharmacists -Monitoring of internal and external laboratory turnaround time - Emergency department toxicology analyzer
2. Inappropriate high doses and erratic or confusing dosing	- Medical Grand Rounds - Educational pharmacy newsletter - Adoption of "mg/h" as standardized format for aminophylline ordering - Purchase of commercially prepared aminophylline with standardized concentration of 1 mg per 1 ml
3 Overlooked toxicity symptoms and signs	- Physician and nurse education - Patient education

4. Recurrent toxicity	- Campaign to increase inclusion of ADRs on chart problem lists - Improved documentation of drug reactions on discharge summary and more readily available computer report of summary - Improved discharge patient education
5. Emergency department giving additional doses to already toxic patients	-Withholding of aminophylline until level is known - Purchase of level annalyzer emergency department
6.Interacting drugs, overlapping	- New inpatient pharmacy computer system to include features to screen for drug interactions and overlap
7.Narrow therapeutic toxic margin	-Encouragement of use of inhaled beta-agonists and steroids as first-line therapy