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Sustained Release Theophylline Preparations
Practical Recommendations for Prescribing and Therapeutic Drug Monitoring

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Summary

Theophylline is an important antiasthmatic medication which has bronchodilator properties. With increased understanding of the relationships of serum theophylline concentration and effect, both adverse and beneficial, oral dosage forms were developed to provide consistent serum theophylline concentrations with the benefit of convenient dosage intervals for long term use.

Since factors such as concurrent disease states, drug interactions and age have a profound effect on theophylline disposition, relatively sophisticated dosage guidelines have evolved. Theophylline is in fact a model drug for the application of pharmacokinetic principles to the individualisation of a treatment regimen.

The purpose of this discussion is to review the relationship of serum theophylline concentration and pharmacodynamic effect and the special properties of oral sustained release theophylline formulations, and to provide a practical approach to prescribing theophylline. Guidelines are provided on the use of serum theophylline concentrations to individualise the theophylline dose, with an analysis of available techniques to monitor theophylline.

1. Mechanism of Action

Despite the use of theophyllines as an antiasthmatic medication since the 1930s (Herrmann et al. 1937), a definitive mechanism of action of the drug has not yet been identified. The bronchodilator properties of theophylline were originally attributed to inhibition of intracellular phosphodiesterase which, subsequently, impairs breakdown of cyclic 3′-5′ adenosine monophosphate (cAMP). Accumulation of cAMP results in smooth muscle relaxation (Kolbeck et al. 1979). However, the concentrations of theophylline necessary to significantly inhibit phosphodiesterase would result in a high incidence of adverse effects (Bergstrand 1980).

There are recent data suggesting that a portion of the bronchodilator properties of theophylline may be attributed to a β-adrenergic effect on the airways resulting in smooth muscle relaxation (MacKay et al. 1983). It appears that theophylline has some bronchoprotective action, since it does block the late asthmatic response to inhaled antigen in sensitised patients (Pauwels et al. 1985).

Adenosine, an endogenous neurotransmitter which produces bronchoconstriction in asthmatic patients, is directly antagonised at receptor sites by theophylline (Cushley & Holgate 1985). A potential antiasthmatic effect of theophylline may be due to adenosine antagonism; however, another potent methylxanthine bronchodilator, enprofylline, lacks this effect (Persson et al. 1981).

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

2. Pharmacodynamics of Theophylline

There is a significant relationship between serum theophylline concentrations (STC) and efficacy and toxicity. Efficacy is presently defined in terms of pulmonary function testing, including measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow (FEF), peak expiratory flow rate (PEFR), and vital capacity (VC). Efficacy is also expressed in the potential to block bronchospasm by allergens or bronchoconstrictive agents such as methacholine or histamine. In addition, the ability to reduce other antiasthmatic medications, particularly glucocorticoids, often serves as a measure of efficacy. Theophylline toxicity may range from relatively minor gastrointestinal irritation and sleep disturbance to major effects such as seizures and cardiac arrhythmias.

2.1 Efficacy

To determine the relationship between pulmonary function and theophylline concentration, Jackson et al. (1964) studied 18 patients with either chronic asthma or acute bronchoconstriction. Vital capacity and maximal breathing capacity closely paralleled peak theophylline plasma concentrations, and declined in parallel with this concentration.

Levy and Koysooko (1975) identified the relationship between FEV_1 and theophylline concentration, as derived from the treatment of 49 asthmatic children (Maselli et al. 1970). A statistically significant correlation existed between plasma concentration and percentage improvement in FEV_1. Of interest is the presence of an initial lag period of 1 hour after theophylline administration, apparently due to a delay in its distribution to tissue compartments. In order to also evaluate the relationship of theophylline concentration to effect, Jenne et al. (1972) studied 83 asthmatics and proposed that changes in specific airway resistance correlated to theophylline concentrations. Mitenko and Ogilvie (1973) further explored this relationship in 9 asthmatic patients. Six patients were each given 3 different infusion rates to provide stepwise increases in plasma theophylline concentrations from 5 to 20 mg/L; the other 3 patients received a single infusion rate to produce plasma concentrations of 5 mg/L (in 2 patients) or 10 mg/L (in the remaining patient). A strong statistical relationship was found between theophylline concentrations and both vital capacity and FEV_1: 20 to 42% improvements in FEV_1 were seen with theo-

phylline concentrations of 5 to 20 mg/L, respectively. These studies helped define the presently recognised therapeutic range for theophylline concentrations of 10 to 20 mg/L.

Theophylline also decreases airway hyperreactivity induced by exercise (Ellis 1984). Pollock et al. (1977) studied 12 children with exercise-induced bronchospasm. Mean theophylline concentration was 16 mg/L. Exercise-induced bronchospasm (induced by treadmill testing) was blocked in all children and a decline in theophylline concentration was related to a dimished effect on the prevention of exercise-induced bronchospasm. Similarly, Bierman et al. (1977) studied 21 children with exercise-induced (treadmill) bronchospasm, both after single and multiple doses of theophylline (adjusted to achieve plasma theophylline concentrations of 10 to 20 mg/L), and 20 patients had 20 to 100% inhibition of exercise-induced bronchospasm by all measurements of pulmonary function.

Theophylline also inhibits antigen- and methacholine-induced bronchospasm. McWilliams et al. (1984) demonstrated in 9 patients a statistically significant increase in the provocation dose necessary to produce a 20% decrease (PD_{20}) in forced expiratory volume in the first second of exhalation (FEV_1) or a 25% decrease in forced expiratory flow (PD_{25}), using methacholine or histamine to induce bronchospasm. Theophylline concentrations in these patients averaged 13 mg/L. Inhibition of antigen-induced bronchospasm, and subsequent histamine release by theophylline, was demonstrated by Martin et al. (1980) in 11 subjects, with a statistically significant 5-fold increase in the provocative dose of the allergen needed to produce a 20% decrease in FEV_1.

Theophylline also inhibits bronchoconstriction that occurs several hours after allergen challenge in sensitive asthmatics. Pauwels et al. (1985) administered aerosolised allergens to susceptible patients and measured the degree of bronchoconstriction after placebo or theophylline coadministration. Theophylline significantly decreased both the immediate (0 to 2 hours), and especially the late phase (3 to 6 hours) bronchoconstrictive response to allergen challenge at steady-state concentrations of approximately 10 mg/L.

Theophylline may also affect dosage of other antiasthmatic medication. Nassif et al. (1981b) demonstrated that maintaining theophylline concentrations between 10 and 20 mg/L led to a decrease in required inhaled beclomethasone use and prednisone bursts, as well as exercise-induced bronchospasm, in steroid dependent asthmatics.

2.2 Toxicity

Toxicity from theophylline appears to be both concentration dependent and independent. Jenne et al. (1972) found that all toxicity, primarily consisting of nausea, vomiting and anorexia, occurred in patients with concentrations greater than 13 mg/L, and was especially common in patients with concentrations greater than 20 mg/L. Stimulation of vomiting centres and gastrointestinal acid secretion was postulated as the cause. One episode of seizures was described in conjunction with a high theophylline concentration, as was a report of atrial arrhythmia. Zwillich et al. (1975) likewise described 8 patients with theophylline concentrations ranging from 25 to 70 mg/L in whom seizures and 4 deaths occurred. Of major concern in these patients was the absence of gastric complaints preceding the onset of seizures.

Concentration-independent effects of theophylline have also been reported. Hendeles et al. (1978) identified nervousness, nausea, and CNS stimulation at the start of theophylline therapy which resolved with continuous therapy. Since theophylline decreases gastroesophageal sphincter tone (Goyal & Rathan 1973), this may contribute to the increased incidence of gastroesophageal reflux in asthmatic patients. Of recent concern is the potential for theophylline to cause behaviour changes. Furukawa et al. (1984a) noted that parents of children taking theophylline could identify school behaviour problems. A follow-up study (Furukawa et al. 1984b) of 6 of these children noted changes in attention, concentration and memory during theophylline treatment. Improvement was observed when theophylline therapy was discontinued.

Springer et al. (1985) evaluated the psychological effects of sodium cromoglycate (cromolyn sodium) and sustained release theophylline. A battery of tests was administered; only one test (visual spatial planning) was significantly affected in the theophylline group, and then only in those patients with a lower IQ. No relationship was apparent between test scores and theophylline concentration.

Rachelefsky et al. (1986) studied 20 mild asthmatics in a double-blind, randomised, parallel trial of theophylline *versus* placebo. Parental and formal psychological evaluations could not distinguish between the two treatments. Teachers, however, recognised differences in behaviour and attention between treatment groups. Effects of theophylline on behaviour is an important consideration and available data on this subject have been recently reviewed (Weinberger et al. 1987). There is no doubt that theophylline has the potential to affect learning and behaviour in some patients; however, the frequency and magnitude of effect is not known. Nevertheless, patients with recognised changes in behaviour, despite careful titration of the theophylline dose, should be treated with alternative medications such as β-adrenergic agonists, sodium cromoglycate or aerosol corticosteroids.

3. Pharmacokinetics

3.1 Absorption

Absorption characteristics of a dosage formulation are usually described by the rate and extent of drug absorption. Theophylline absorption from liquids or plain tablets is rapid and complete (Hendeles et al. 1977b; Upton et al. 1980), facilitating rapid achievement of therapeutic plasma concentrations. Many patients, such as children (Ellis et al. 1976) and smokers, have a rapid elimination which produces a rapid decline in theophylline concentrations, resulting in large fluctuations of drug concentration in the plasma (high peaks, low troughs) and clinical response. This necessitates frequent dosage administration, which is inconvenient and incompatible with a normal lifestyle.

Sustained release products are designed to decrease the rate (not extent) of absorption. This decreases peak-to-trough fluctuations, allowing less frequent dosage administration, and improves compliance. The rate of absorption of theophylline is partially determined by its rate of dissolution, which is controlled by coated drug particles. The thickness of the coating alters the dissolution rate. The coated particles, or beads, may be placed in a capsule or embedded in a tablet. The ideal dosage form should provide a constant ('zero-order') rate of drug dissolution and consequent absorption, resembling a constant-rate 'infusion'. Unfortunately, there is a great deal of variability in absorption characteristics among sustained release products in terms of rate, and also extent, of absorption. This is of particular concern for a drug such as theophylline with a narrow margin of safety.

3.1.1 Intra- and Intersubject Variability in Theophylline Absorption

Absorption of theophylline from most formulations is relatively reliable in most patients. Recently, however, several studies have demonstrated intrasubject variability in absorption which may affect the efficacy of theophylline. Intrasubject variability in theophylline absorption was investigated by Dederich et al. (1981) in 8 subjects who received 2 single doses of 'Theo-Dur' (Key Pharmaceuticals) tablets and 'Slo-Phyllin Gyrocaps' (William H. Rorer, Inc.). Results indicate a more rapid rate of absorption for 'Slo-Phyllin Gyrocaps', and complete extent of absorption for both 'Theo-Dur' and 'Slo-Phyllin Gyrocaps'. Large intrasubject variability was apparent for measurements of time to peak plasma concentration, absorption rate constant, time until 90% absorbed, and area under the plasma concentration *versus* time curve (AUC) for both products. The observed inconsistency in serum theophylline concentrations from day to day in certain patients prompted a study by Rogers et al. (1985) to define the aetiology of this phenomenon. Eight children were studied in order to determine whether changes in clearance or absorption were responsible for erratic plasma concentrations observed during routine monitoring. Clearance remained unchanged, as determined by a constant intravenous infusion of aminophyl-

line. Oral studies demonstrated large inter- and intrasubject variabilities in time to peak (0 to 12 hours) and trough, and in fluctuations in theophylline concentrations. It was therefore concluded that inconsistencies in the rate of theophylline absorption were responsible for the erratic concentration-time profiles observed in these children. A circadian rhythm for theophylline absorption has also been described (Scott et al. 1981), and attributed to a decreased rate of theophylline absorption at night.

Inter- and intrasubject variability in sustained release theophylline absorption was also investigated by Pollack et al. (1984) by comparing the absorption characteristics of 2 sustained release theophylline preparations (a capsule and a tablet) in 12 volunteers. Although the extent of absorption was consistently complete, the rate of absorption varied considerably, especially within the first 4 hours following dosage administration. Therefore, there are a number of host factors such as gastrointestinal transit time, posture, presence of food, etc, which are related to gastrointestinal physiology which may influence the rate of theophylline absorption.

3.1.2 Sustained Release Delivery Systems

Effect of Food on Absorption Characteristics

Extent of absorption is determined utilising a single dose, and the mean rate and extent of absorption is used to estimate steady-state concentrations with multiple doses by applying computer simulations. Study doses are typically given to fasting subjects, thus negating the effect of food on absorption. Therefore the estimates of extent of absorption during these special conditions may not completely reflect the true extent of absorption during routine treatment. Table I provides a list of sustained release theophylline products whose extent of absorption is complete during fasting conditions.

Food alters the rate and extent of absorption of certain sustained release theophylline preparations. Significant alterations in theophylline absorption occur with 'Uniphyl' and 'Theo-24', two preparations designed for once daily administration, and 'Theo-Dur Sprinkle', a preparation intended for twice daily administration in children. Karim et al. (1985) showed an increase in 'Uniphyl' bioavailability from 53% to 96% in adults during fasting and non-fasting conditions, respectively; however, the opposite effect was noted with 'Theo-Dur Sprinkle', where bioavailability was reduced to approximately 50% in the presence of food. Similarly, Pedersen and Møller-Petersen (1984) described a delay in absorption of 'Theo-Dur Sprinkle', and a decrease in bioavailability from 91% to 44% in fasting and non-fasting children, respectively (see table II).

Choice of Product and Dosage Interval

Absorption characteristics of sustained release theophylline products, and the patient's theophylline clearance determine how frequently the dose should be administered. Slowly and completely absorbed products may be administered every 12 or 24 hours in adult non-smokers. Children and smoking adults usually require 8- or 12-hour dosage intervals to maintain acceptable peak/trough fluctuations. Computer simulations developed by Hendeles et al. (1984) were used to predict fluctuations in serum theophylline concentrations with known absorption characteristics of various products and mean half-lives in children and smoking adults (3.7 hours), as well as non-smoking adults (8.2 hours). Individual formulations and predicted dosage intervals for these products, based on these computer simulations, are summarised in table I.

Products for Once Daily Dosing

Several sustained release theophylline products have recently been approved for once daily dosing. As discussed previously, dosage frequency is dependent on both formulation (rate of dissolution) and the patient's elimination parameters. For patients with slower elimination and long half-lives (e.g. adult non-smokers), theophylline products may be given every 12 or 24 hours. The newly formulated ('once-daily') products include 'Theo-24' ('Pulmo-timelets') and 'Uniphyl' ('Uniphyllin'). Variations in bioavailability under fasting condi-

tions, compared with administration with food, have been reported for both formulations (Hendeles et al. 1985; Karim et al. 1985). A recent report suggests that food effects may not occur with another formulation, 'Noctelin' (Pedersen & Steffensen 1987). Once-daily administration may be appropriate in patients with slower clearance or with the ability to tolerate wider peak/trough fluctuations; however, additional studies are needed to assure efficacy and safety of these products in patients with rapid theophylline metabolism, especially children.

3.2 Distribution

Within 1 hour after an intravenous injection, tissue concentrations (including lung) achieve an equilibrium with the concentration of theophylline in serum, suggesting relatively rapid distribution (Levy & Koysooko 1975). This 1-hour time delay

Table I. Theophylline products with complete absorption during fasting conditions[a] (updated and reprinted with permission from Hendeles et al. 1984)

Type/source	Brand names dosage intervals[a]	Dosage interval selected (hours)		Type/source	Brand names dosage intervals[a]	Dosage interval selected (hours)	
		children, adult smokers	adult non-smokers			children, adult smokers	adult non-smokers
Plain tablets							
W.H. Rorer, Riker Laboratories, Johnson & Johnson	'Slo-Phyllin' 'Theolair' 'Theophyl'	< 8	12	Key Pharmaceuticals	'Theo-Dur Sprinkle'	12	12
				K-V Laboratories	'Elixophyllin SR' 'Theobid' 'Theovent'	8	12
Bead-filled capsules							
Central Pharmacal Co	'Physpan' 'Qibron-BID' 'Theoclear LA' 'Theon-300' 'Theophylline Anhydrous TD' 'Theospan SR'	8	12	W.H. Rorer	'Slo-Bid Gyrocaps'	12	12
				Riker Laboratories	'Noctelin'	24	24
				Slow release tablets			
				Norwich-Eaton	'LaBID'	8	12
				Cord Laboratories	'Constant-T'	8	12
				Key Pharmaceuticals	'Pulmi-Dur' 'Theolin-Retard' 'Sustaire' 'Theo-Dur'	12	12
Cord Laboratories	'Afonilum Retard' 'Bronkodyl S-R' 'Elixophyllin SR' 'Slo-Phyllin Gyrocaps' 'Theophyl-SR'	8	12				
				Mead Johnson	'Quibron-T/SR'	8	12
				Mundipharma	'Phyllocontin' 'Phyllotemp'	8	12
Graham Laboratories	'Aerolate' 'Somophyllin-CRT' 'Somophyllin-12'	8	12	Riker Laboratories	'Nuelin-SR' 'Respbid' 'Theolair-SR'	8	12
				Warner-Lambert	'Choledyl SA'	8	12

a Computer simulations were performed (Hendeles et al. 1984) to predict fluctuations in steady-state theophylline concentrations for patients with half-lives of 3.7 hours (children and adult smokers) and 8.2 hours (adult non-smokers), for dosage intervals of 8 and 12 hours. Fluctuations < 150% were considered acceptable for the given dosage interval. Calculated fluctuations are converted to dosage intervals which are likely to provide acceptable fluctuations in theophylline concentrations.

Table II. Effect of food on the rate and extent of theophylline absorption from sustained release preparations (updated version reprinted with permission from Petty et al. 1987)

Product	Amount absorbed fasting (%)	Amount absorbed with food (%)	Rate of absorption with food	Clinical significance[a]	Reference
Twice daily preparations					
'Theo-Dur' tablets	93	93	No effect	0	Sips et al. (1984)
'Somophyllin-CRT'	96	106	No effect	0	Pedersen & Møller-Petersen (1985)
'Slo-Bid Gyrocaps'	85	85[b]	Slight decrease	0	Weinberger, personal communication[c]
'Theo-grad'	64	90	Decreased	+	Lagas & Jonkman (1983)
'Theolair-SR', 'Nuelin'	ND[d]	No change[e]	Decreased	?	Pedersen & Møller-Petersen (1982)
'Theo-Dur Sprinkle'	91	44	Decreased	++	Pedersen & Møller-Petersen (1984)
Once-daily preparations					
'Uniphyl', 'Uniphyllin'	56	91[b]	Slight increase	+	Karim et al. (1985)
'Theo-24', 'Pulmo-timelets'	71	111[b]	6-8 hours post-dose marked increase	++	Hendeles et al. (1985)
'Noctelin'	102	88	Slight decrease	0	Pedersen & Steffensen (1987)

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 In two of three lots examined by Dr Weinberger, bioavailability fasting was 100%. The value of 85% in the food study may represent lot-to-lot variability.

d ND = no data available.

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

in bronchodilator effect occurs even after oral dosing with non-sustained release oral dosage forms (Richer et al. 1982). Physicochemical properties of theophylline, namely the octanol : water partition coefficient (an indicator of lipid solubility), indicate that the drug has an equal affinity for water and lipids (Leo et al. 1971). This property – along with relatively low protein binding [approximately 40% (Shaw et al. 1982)] – results in extensive distribution of this drug. Theophylline also distributes into breast milk in a milk : serum ratio of 0.63 to 0.87 during long term therapy (Yurchak & Jusko 1976). Theophylline can be used during breast feeding, but only with careful observation for signs or symptoms of toxicity in the infant since elimination in newborns and infants less than 6 months is very slow. However, there are several reports of theophylline toxicity in breast-fed infants. Theophylline is also distributed to saliva in concentrations approximately 60% of serum theophylline concentrations (Levy et al. 1974), but the ratio is too inconsistent to utilise saliva concentrations as an indicator of serum theophylline concentration (Hendeles et al. 1977a). Since theophylline doses have limited distribution to fat tissue, loading doses in obese patients (> 30% above ideal bodyweight) should be calculated with consideration of excess bodyweight; however, maintenance doses should be based on ideal bodyweight (Zell et al. 1985).

3.3 Elimination

Theophylline is extensively metabolised in the liver by the hepatic cytochrome P450 mixed function oxidase system, and recent studies have detailed the multiple pathways – a mixture of first-order and capacity-limited processes (Tang-Liu et al. 1981). Several enzymes are responsible for these pathways, and contribute to potential drug interactions. Theophylline may indeed be a 'window'

Table III. Clinically relevant drug interactions for theophylline

	Change in elimination[a]	Likelihood of necessity for dose adjustment[b]	Reference
Increase clearance			
Phenytoin	2-fold increase	+	Marquis et al. (1982)
Carbamazepine	2-fold increase	++	Rosenberry et al. (1983)
Phenobarbitone	Variable	+/− variable, monitor STC	Landay et al. (1978)
Valproic acid	Not studied	0	
Rifampicin	1.8-fold increase	+	Hauser et al. (1983)
Marijuana and/or tobacco smoking	1-2-fold increase compared to population averages	+	Jusko et al. (1978)
Decrease clearance			
Erythromycin	1.4-fold decrease	+/− variable, monitor STC	Prince et al. (1981); LaForce et al. (1981)
Troleandomycin	2-fold decrease (250mg TAO qid)	++	Weinberger et al. (1977)
	1.2-fold decrease (250mg TAO qod)	+/− variable, monitor STC	Wald et al. (1986)
Oral contraceptives	1.4-fold decrease	+ potentially variable depending on oestradiol content of contraceptive	Gardner et al. (1983)
Propranolol	1.7-fold decrease	+/− transient effect, may not be clinically relevant; propranolol is contraindicated in patients with reactive airways disease	Conrad & Nyman (1980)
Cimetidine	1.5-fold decrease (1.2 to 2-fold range)	++, occurs within 24 hours. Decrease dose *a priori*. Alternatively, use ranitidine as H_2-antagonist	Reitberg et al. (1981); Powell et al. (1984); Sorkin & Darvey (1983)

a Change in elimination is estimated from the average value in the report cited.

b Likelihood of necessity for dosage adjustment represents the clinical relevance by estimating the potential need for dosage adjustments as a result of the interaction. These are general guidelines and do not replace the need for serum theophylline concentration measurement, dosage adjustments and monitoring the patient for breakthrough asthma or symptoms of theophylline toxicity.

Abbreviations: STC = serum theophylline concentration; TAO =troleandomycin; qid = 4 times daily; qod = every other day.

into hepatic oxidative function (Jenne 1982). The various routes of metabolism are not only susceptible to drug interactions (table III), but are also impaired in patients with liver disease (Mangione et al. 1978) or passive hepatic congestion due to congestive heart failure (Powell et al. 1978). Dose-dependent or zero-order elimination is seen in some patients. With higher serum theophylline concentrations, elimination of theophylline is slower in children (Weinberger & Ginchansky 1977), as well as adults. This results in a larger than proportional increase in serum theophylline concentration for a given increase in dosage. For example, if the dose is increased by 20%, steady-state serum theophylline concentration may increase 40 to 100%, depending on the metabolising enzyme capacity. This phenomenon usually occurs with serum theophylline concentrations exceeding 20 mg/L, but may occur in approximately 15% of children with concentrations less than 20 mg/L (Weinberger & Ginchansky 1977). Therefore, theophylline dosage adjustments generally should not exceed increments of 25% without an evaluation of efficacy and signs of toxicity.

Ideally, dosage adjustments should be followed with a measurement of serum theophylline con-

centration within 2 to 3 days, especially if it is necessary to exceed recommended doses.

3.3.1 Age and Theophylline Elimination

Theophylline metabolism is significantly reduced during the newborn period (Aranda et al. 1976), and increases slowly during the first year of life to reach the maximum, in relation to bodyweight in children aged 1 to 9 years (Ellis et al. 1976; Nassif et al. 1981a). With increasing age, clearance decreases such that adolescents' rates are similar to those of non-smoking, otherwise healthy, young adults (see table IV).

Detailed reviews of the disease states and concomitant medication which affect theophylline disposition are available (Hendeles et al. 1986; Jonkman & Upton 1984), and provide the interested reader with information on the individual factors which affect theophylline disposition.

Table IV. Theophylline elimination half-life and average dose requirement to achieve serum theophylline concentrations of 10 mg/L

Age	Half-life (h, mean ± SD)	Average dosage (mg/kg/day)	Reference
Premature newborn	30 ± 7	2.0-3.0	Aranda et al. (1976)
Infants			
< 6 months	14 ± 4	Dosage mg/kg/day = 0.2 (age in wks) + 5.0	Nassif et al. (1981a)
6 months to 1 year	6 ± 1	20-24	Rosen et al. (1979)
Children			
1-4 years	3.4 ± 1.1	20	Loughnan et al. (1976)
4-12 years		20	
12-17 years	3.7 ± 1.1	16	
Adults			
Healthy, non-smoking	8.1 ± 2.4	13	Jusko et al. (1978)
Elderly, non-smoking	9.8 ± 4.1	13	Antal et al. (1981)

4. Application of Serum Theophylline Concentration Monitoring

In most clinical situations, decisions regarding theophylline dosage adjustments are based on a limited number of serum theophylline concentration measurements. There are several important considerations for proper interpretation and application of serum theophylline concentration measurements to theophylline dosage adjustments (fig. 1).

Proper interpretation of a single serum theophylline concentration measured during an office visit requires background information that is patient specific. As a minimum, this information should include, total daily dose in relation to bodyweight, specific formulation of theophylline, times that doses are usually administered, timing of sample relative to dose, and any concomitant medication or disease. At this point, the physician should determine whether any of these factors have changed recently. Specific questions to review include: Is the patient compliant? Is the patient experiencing or at risk for an adverse effect? If the serum theophylline concentration that is obtained gives unexpected results, a systematic review should be conducted prior to a change in the dosing scheme (fig. 2).

The adequacy of the theophylline regimen in terms of providing the desired level of protection from the signs and symptoms of chronic asthma is also important. Questions to be asked of the patient in this regard should include: Are symptoms controlled? Are symptoms more frequent at the end of a dosage interval? Are symptoms worse at night? These questions may provide the physician a better insight for the appropriate time to obtain a serum theophylline concentration measurement.

4.1 Influence of Dosage Regimen on Sample Collection

The formulation of oral theophylline and the interval between doses will also influence the optimal time to obtain a serum theophylline concentration. Liquids and plain non-sustained release

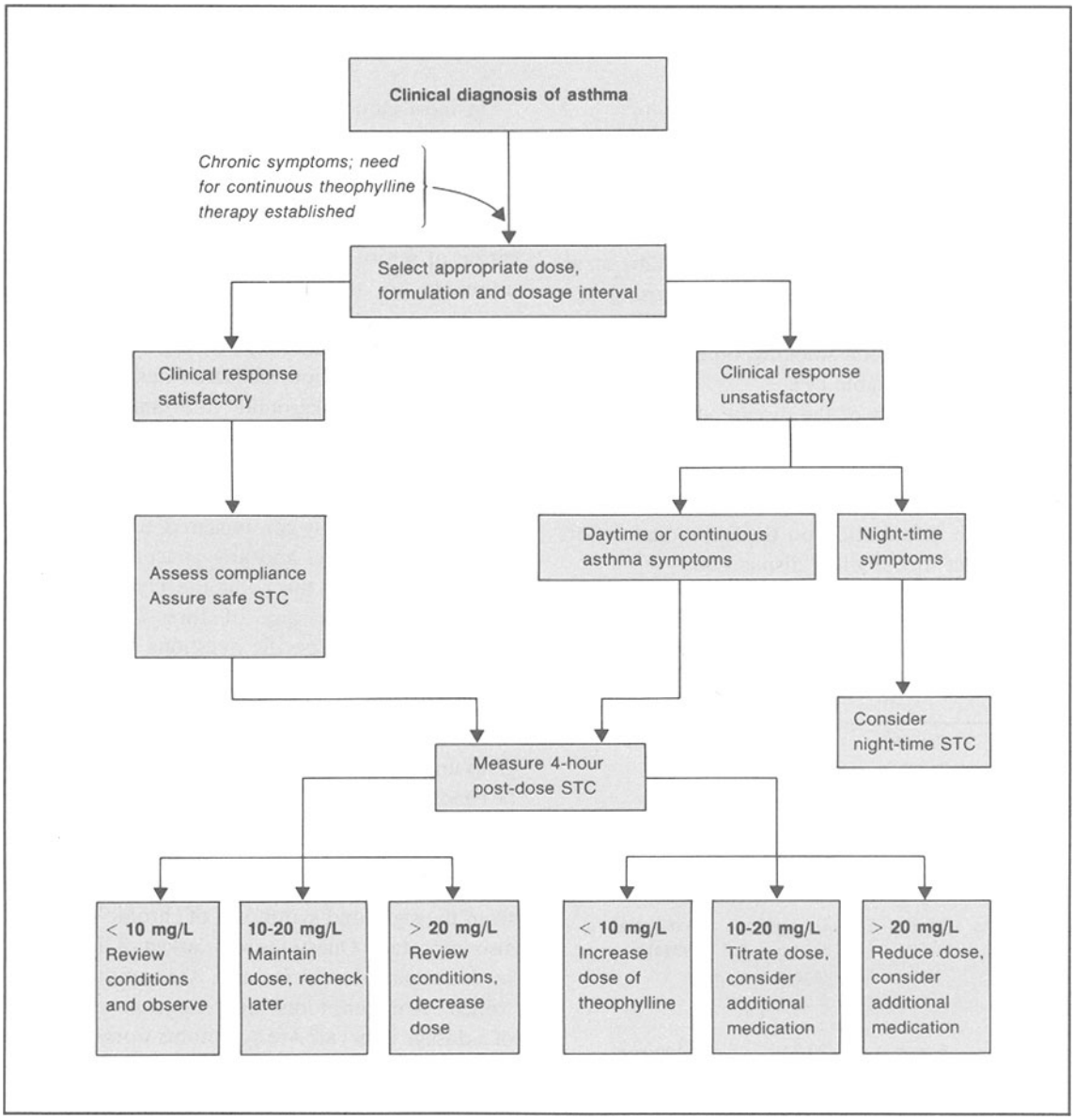

Fig. 1. Scheme for establishing optimal oral sustained release theophylline dosage which accounts for clinical response and serum theophylline concentration (STC). Frequency of measurement of serum theophylline concentration depends upon clinical response, changes in concurrent disease states, and potential drug interactions. Once final dosage adjustments are arrived at, serum theophylline concentrations may be checked every 6 months in patients who are well controlled.

formulations will provide maximum serum theophylline concentrations 1 to 2 hours after administration (Hendeles et al. 1977b). The lowest serum theophylline concentration is usually immediately prior to the next dose. The degree of temporal variation that is seen with these formulations may not

be as marked as with sustained release theophylline, although this has not been thoroughly evaluated.

With sustained release formulations such as 'Slo-Bid Gyrocaps' (William H. Rorer, Inc.) or 'Theo-Dur' tablets (Key Pharmaceuticals), there is significant temporal variation in the patterns of serum theophylline concentrations (Rogers et al. 1987; Scott et al. 1981). As a result of these patterns, the maximum serum theophylline concentration measured for the entire 24-hour period typically occurs 2 to 6 hours after the morning dose. The lowest serum theophylline concentration most frequently is observed at or just following the evening dose of sustained release theophylline. It is important to note that predose serum theophylline concentration measured in the morning is significantly higher than the true minimum serum theophylline concentration, and overestimates this value by 1 to 4 mg/L. Age-related differences in the serum theophylline concentration-time profile are also obtained with reliable preparations administered twice daily (fig. 3). This is likely related to differences in the rate of elimination and gastrointestinal

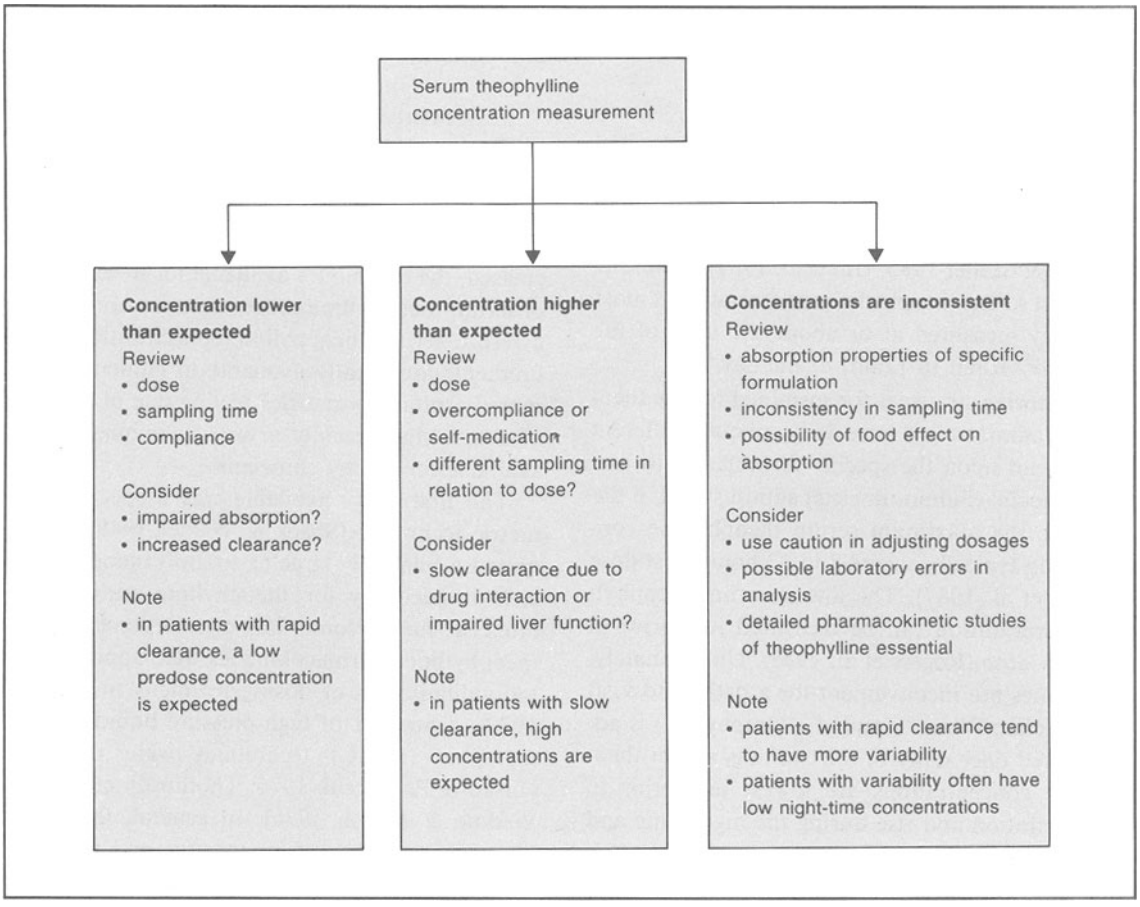

Fig. 2. Unanticipated serum theophylline concentrations are observed in some patients. The potential reasons must be reviewed, and decisions regarding final dosage adjustments should be based upon the findings. In some patients, variations in serum theophylline concentrations are excessive ($\geq$ 20 and $<$ 10 mg/L on the same regimen) and alternatives to theophylline therapy should be considered.

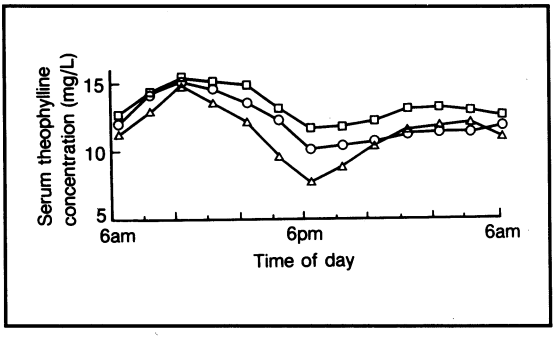

Fig. 3. Average serum theophylline concentrations *versus* time for asthmatic children aged 1 to 6 years (△, n = 22), 7 to 11 years (○, n = 24), and 12 to 18 years (□, n = 49). Equal doses of 'Slo-Bid' or 'Theo-Dur' were administered at 6am and 6pm. Note the temporal pattern, with serum theophylline concentrations higher after morning doses compared with those following evening doses (Hill et al. 1987).

physiology among the various age groups. For patients on 8-hourly regimens, the rate of theophylline absorption may be slower in the evening (Haltom & Szefler 1985; Hill et al. 1987); therefore, the lowest serum theophylline concentration is most accurately measured at or about the time of the third dose (10pm to 12am) of the day.

Monitoring strategies for sustained release theophylline administered once daily are quite different and depend upon the specific formulation in use. For 'Theo-24' (Pulmo-timelets) administered in the morning, the maximum serum theophylline concentration typically occurs 8 to 12 hours post dose (Rogers et al. 1987). The lowest serum theophylline concentration can be measured just prior to the daily dose (Rogers et al. 1987). Unfortunately, these times are inconvenient for a patient to visit the clinician. When 'Uniphyl' ('Uniphyllin') is administered once daily in the evening, serum theophylline concentrations are lowest just prior to administration and rise during the night-time and early morning hours to reach a maximum mid-morning. This dosage scheme may have advantages in providing the highest serum theophylline concentrations during the night for patients with nocturnal worsening of asthma, and the maximum serum theophylline concentrations are achieved at a time that is more convenient to measure during clinician visiting hours.

For patients who have excessive fluctuation in serum theophylline concentrations over a dosage interval, it is reasonable to reduce the time between doses, keeping the total amount of drug administered per day the same. Excessive fluctuation is present when subtherapeutic serum theophylline concentrations occur at the end of a dosage interval, and maximum serum theophylline concentration is approaching 20 mg/L. This is assessed by measuring the highest and lowest serum theophylline concentration on a particular regimen. More importantly, it is assessed clinically by determining if 'breakthrough' wheezing is occurring at the end of a dosage interval.

5. Measurement of Serum Theophylline Concentration

As awareness of the benefits of achieving a target range for serum theophylline concentrations increased, the techniques available for measurement of serum theophylline concentration improved. As a result, serum theophylline concentration measurements are readily available to clinicians, with most hospital laboratories having one of a variety of assays. More recently, several techniques are now available for use by clinicians.

The first assay available was a spectrophotometric technique (Shack & Waxler 1949), but required a relatively large (1 to 2ml) blood sample, lacked specificity for theophylline and incorporated a cumbersome laboratory procedure. As theophylline pharmacokinetics were applied to the individualisation of dosing regimens in the mid-1970s, a number of high-pressure liquid chromatographic (HPLC) techniques were developed (Jusko & Poliszczuk 1976; Thompson et al. 1974; Weddle & Mason 1976). In general, these techniques are rapid, precise, specific, and require as little as 20 to 100μl of serum or plasma. Subsequently, other methods were developed with emphasis on quantitation of major and minor metbolites for research purposes (Muir et al. 1980). About the same time, Broussard (1981) published

a 'selected method' for serum theophylline concentration determination. This widely adapted method was free of many potential drug interferences. Unfortunately, it was later demonstrated that a metabolite of caffeine, paraxanthine (1,7-dimethylxanthine), caused significant interference (Jonkman et al. 1982). This interference results in a 30% overestimation of actual serum theophylline concentration, and potential subtherapeutic dosage adjustments. In general, the major disadvantages of HPLC techniques are the cost of the initial equipment and the laborious nature of the procedures. Advantages are the low cost per assay for reagents and supplies for processing large numbers of samples.

In 1978, a new homogeneous enzyme-multiplied immunoassay technique (EMIT®, Syva, Palo Alto, CA) was introduced. This procedure is ideally suited to the clinical chemistry laboratory because of its precision, specificity, and ease of analysis (Koup & Brodsky 1978). This procedure requires moderate analytical skill, reagent and initial equipment costs. Currently, several large automated serum chemistry analysers utilise 'EMIT' reagents to measure serum theophylline concentration. The fluorescence polarisation immunoassay (Abbott TDX®, Abbott Laboratories, North Chicago, IL) is a recently developed system which is also very specific and precise. This method was developed to provide assays for virtually all drugs that require serum concentration monitoring, as well as a number of other serum chemistries. This highly automated system provides short turn around time with only minimal technical skill. Due to the cost of this system, it is only practical for commercial or hospital laboratories. Another rapid immunoassay, 'Seralyzer' (Ames, Elkhart, IN), is available for emergency room or office measurements of serum theophylline concentration. This simple method is well suited for use in a physician's office due to low initial cost, ease of operation, less than 5 minutes analytical time, and only 50μl serum sample requirement. It can also perform analyses for potassium, glucose, blood urea nitrogen, phenytoin, phenobarbitone and others (Hendeles & Hill 1988). The precision is less than that provided by other immunoassays or HPLC, but is certainly adequate for clinical serum theophylline concentration monitoring purposes.

In 1986, a method for serum theophylline concentration measurement requiring no instrumentation was developed: 'Acculevel' (Syntex Medical Diagnostics, Palo Alto, CA) combines immunoassay and thin layer chromatographic techniques. This assay system gives relatively accurate and precise results with a small (12.5μl) whole blood requirement which may be obtained from a fingerstick technique (Vaughn et al. 1986). Results for serum theophylline concentration measurements compare favourably with 'EMIT', 'TDX' and HPLC. The techniques are simplified such that office personnel may be easily and adequately trained. The total time required for analysis is less than 12 minutes. Currently, the approximate retail cost of a single 'Acculevel' kit is $US20.00. In selected situation we have trained patients and parents to perform assays at home. This should only be attempted with the understanding that all results are reported to the clinician and reasonable steps taken to assure proper technique and quality control.

The precision of any procedure is dependent upon proper technique. Excellent performance under experimental conditions is not sufficient, since poor performance has been reported even from clinical laboratories (Bonham et al. 1980). The reproducibility of any assay should be assessed by the clinician relying on results upon which therapeutic decisions are based. With the availability of methods for determination of serum theophylline concentration in the office, clinicians responsible for the procedure should take steps to provide quality assurance. Proper training of office personnel and the use of a referral laboratory to provide periodic confirmation of a patient's results are a minimum. It may be best to assay patient specimens in duplicate until the clinician is comfortable with the test results.

6. Conclusion

Several enzyme systems are responsible for theophylline metabolism, and these pathways contribute to the multiple drug interactions that are

observed with the drug. The various routes of metabolism are not only susceptible to drug interactions, but are also impaired in patients with liver disease and with passive hepatic congestion due to congestive heart failure, and can become saturated, resulting in dose-dependent or zero-order elimination in some patients. Detailed reviews of the disease states and concomitant medications which affect theophylline disposition are available, and provide the interested reader with specific information on the individual factors which affect theophylline disposition (Hendeles et al. 1986; Jonkman & Upton 1984).

There is, unfortunately, a great deal of variability in the absorption characteristics among sustained release products in terms of rate and, to some degree, extent of absorption. Most slowly and completely absorbed formulations may be administered every 12 and, occasionally, every 24 hours in adult non-smokers. Children and smoking adults may require 8- to 12-hour dosage intervals (see table I). Once-daily administration may be appropriate in some patients who have slower clearances, or the ability to tolerate wider peak-to-trough fluctuations in serum theophylline concentration; however, additional studies are needed to assure efficacy and safety of these products in patients with more rapid metabolism, especially children. For patients with excessive fluctuation in serum theophylline concentrations over a dosage interval, or over a 24-hour period, it is reasonable to reduce the time between doses, keeping the total amount of drug administered per day the same.

There have been tremendous contributions to understanding the rational use of theophylline in the last 15 years. As knowledge and experience were gained, the popularity of the drug increased. The clinician can use theophylline effectively as long as the many factors which affect its use are appreciated. Detailed approaches to therapy which include specific guidelines for individual patients are now available. Theophylline will likely remain an important antiasthmatic preparation for many years to come, and it is likely that additional information regarding its use, as well as new, more convenient dosage forms, will appear in the near future.

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