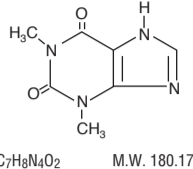


Theophylline Extended-Release Tablets

Rx only

DESCRIPTION:

Theophylline is structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-Purine-2, 6-dione, 3,7-dihydro-1, 3-dimethyl-, and is represented by the following structural formula:



This product allows a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see **DOSEAGE AND ADMINISTRATION** section for description of appropriate patient populations).

Each extended-release tablet for oral administration contains either 100 mg or 200 mg or 300 mg or 450 mg of anhydrous theophylline. Tablets also contain as inactive ingredients: hypromellose, lactose monohydrate, colloidal silicone dioxide, magnesium stearate.

CLINICAL PHARMACOLOGY: Mechanism of Action:

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (i.e., bronchodilation) and suppression of the response of the airways to stimuli (i.e., non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE II and, to a lesser extent, PDE IV) while non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms, that do not involve inhibition of PDE III or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE III (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow).

Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Serum Concentration-Effect Relationship:

Bronchodilation occurs over the serum theophylline concentration range of 5-20 mcg/mL. Clinically important improvement in symptom control has been found in most studies to require a peak serum theophylline concentrations >10 mcg/mL, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations >20 mcg/mL, both the frequency and severity of adverse reactions increase. In general, maintaining peak serum theophylline concentrations between 10 and 15 mcg/mL will achieve most of the drug's potential therapeutic benefit while minimizing the risk of serious adverse events.

Pharmacokinetics:

Overview: Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues and is extensively metabolized in the liver. The pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight or other demographic characteristics. In addition, certain concurrent illnesses and alterations in normal physiology (see Table I) and co-administration of other drugs (see Table II) can significantly alter the pharmacokinetic characteristics of theophylline. Within-subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. It is, therefore, recommended that serum theophylline concentrations be measured frequently in acutely ill patients (i.e., at 24-hr intervals) and periodically in patients receiving long-term therapy, e.g., at 6-12 month intervals. More frequent measurements should be made in the presence of any condition that may significantly alter theophylline clearance (see **PRECAUTIONS, Laboratory Tests**).

Population Characteristics	Total body clearance* mean (range)†† (mL/kg/min)	Half-life mean (range)†† (hr)
Age		
Premature neonates postnatal age 3-15 days	0.29 (0.09-0.49)	30 (17-43)
postnatal age 25-57 days	0.64 (0.04-1.2)	20 (9.4-30.6)
Term infants postnatal age 1-2 days	NR†	25.7 (25-26.5)
postnatal age 3-30 weeks	NR†	11 (6-29)
Children 1-4 years	1.7 (0.5-2.9)	3.4 (1.2-5.6)
4-12 years	1.6 (0.8-2.4)	NR†
13-15 years	0.9 (0.48-1.3)	NR†
6-17 years	1.4 (0.2-2.6)	3.7 (1.5-5.9)
Adults (16-60 years) otherwise healthy non-smoking asthmatics	0.65 (0.27-1.03)	8.7 (6.1-12.8)
Elderly (>60 years) non-smokers with normal cardiac, liver, and renal function	0.41 (0.21-0.61)	9.8 (1.6-18)
Concurrent illness or altered physiological state		
Acute pulmonary edema	0.33** (0.07-0.245)	19** (3.1-82)
COPD->60 years, stable non-smoker >1 year	0.54 (0.44-0.64)	11 (9.4-12.6)
COPD with cor pulmonale	0.48 (0.08-0.88)	NR†
Cystic fibrosis (14-28 years)	1.26 (0.31-2.2)	6.0 (1.8-10.2)
Fever associated with acute viral respiratory illness (children 9-15 years)	NR†	7.0 (1.0-13)
Liver disease - cirrhosis	0.31** (0.1-0.7)	32** (10-56)
acute hepatitis	0.36 (0.25-0.45)	19.2 (16.6-21.8)
cholestasis	0.66 (0.25-1.45)	14.4 (5.7-31.8)
Pregnancy - 1st trimester	NR†	8.5 (3.1-13.9)
2nd trimester	NR†	8.8 (3.8-13.8)
3rd trimester	NR†	13.0 (8.4-17.6)
Sepsis with multi-organ failure	0.47 (0.19-1.9)	18.8 (6.3-24.1)
Thyroid disease - hypothyroid	0.36 (0.13-0.57)	11.6 (8.2-25)
hyperthyroid	0.8 (0.68-0.97)	4.5 (3.7-5.6)

* For various North American patient populations from literature reports. Different rates of elimination and consequent dosage requirements have been observed among other peoples.

† Clearance represents the volume of blood completely cleared of theophylline by the liver in one minute. Values listed were generally determined at serum theophylline concentrations <20 mcg/mL; clearance may decrease and half-life may increase at higher serum concentrations due to non-linear pharmacokinetics.

†† Reported range or estimated range (mean ± 2SD) where actual range not reported.

NR = not reported or not reported in a comparable format.

** Median

NOTE: In addition to the factors listed above, theophylline clearance is increased and half-life decreased by low carbohydrate/high protein diets, parental nutrition, and daily consumption of charcoal-broiled beef. A high carbohydrate/low protein diet can decrease the clearance and prolong the half-life of theophylline.

Absorption: Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. After a single dose immediate release theophylline of 5 mg/kg in adults, a mean peak serum concentration of about 100 mcg/mL (range 5-15 mcg/mL) can be expected 1-2 hour after the dose. Co-administration of theophylline with food or antacids does not cause clinically significant changes in the absorption of theophylline from immediate-release dosage forms.

Single-Dose Study: (450 mg)

A single-dose, two-way crossover study was conducted in sixteen healthy male volunteers under fasting conditions with one 450 mg tablet being administered at 7 a.m. with a 6 oz. glass of water. No food or liquid (other than water) was allowed for 4 hours after which a standard lunch was served. Mean peak theophylline serum levels (C_{max}) was 6.69 mcg/mL and mean time of peak serum concentration (T_{max}) was 8.31 hours.

(300 mg)

A single-dose crossover study was conducted in twelve healthy male volunteers to compare pharmacokinetic parameters when theophylline extended-release tablets were administered with and without food. Subjects were fasted overnight and received a single 300 mg tablet early the following morning.

When dosing was done under fed conditions, the subjects received a standard breakfast consisting of 2 fried eggs, 2 strips of bacon, 4 oz. hash brown potatoes, 1 slice of toast with a pat of butter, and 8 oz. whole milk 15 minutes pre-dosing. No food was allowed for five hours post-dosing, then a standard lunch was served, at ten hours post-dosing a standard supper was served. Mean peak theophylline serum levels for the two treatments were 3.7 mcg/mL (fasting) and 4.4 mcg/mL (with food). The time of peak serum level varied from subject to subject, occurring from 4 to 14 hours after dosing. However, 92% of the subjects had serum levels at least 75% of the maximum value at 4 to 8 hours after dosing, during each phase.

Thus, blood samples taken 4 to 8 hours post-dosing should reference the peak serum level for most patients. The mean T_{max} was 6.2 hours (fasting) and 8.7 hours (with food). The respective AUC (0-∞) for these treatments were 73.3 mcg • hr/mL and 82.2 mcg • hr/mL, respectively.

Multiple-Dose Study: (300 mg)

A multiple-dose, steady-state study was conducted under fed conditions. Three high fat content meals were served at 6:30 a.m., 12 noon and 6:30 p.m. Nineteen normal subjects were dosed at 300 mg every 12 hours (7 p.m. and 7 a.m.) for eight doses. Dosing began one-half hour after the evening meal with the test dose occurring one-half hour after breakfast. At steady-state, the mean peak concentration was 8.8 mcg/mL and the mean trough concentration was 5.9 mcg/mL.

The time of peak concentration (T_{max}) was 6.2 hours. The average percent fraction of fluctuation [(C_{max}-C_{min}/C_{min}) x 100] was 49% for this formulation and dosing regimen.

The subjects used for this study exhibited a mean half-life of 8.3 hours (range 5.2-12.2) and mean clearance of 3.5 L/hour (range 2.3-5.6) as determined in a separate single-dose clearance study using 500 mg of immediate-release theophylline, prior to this multiple-dose study.

Once-a-Day Dosing:

A multiple-dose, steady-state study was conducted under fed conditions with once-a-day dosing. Fed conditions were the same as those previously cited. Sixteen subjects were dosed as 2 x 300 mg tablets every morning at 8 a.m. for five doses. At steady-state, the mean C_{max} was 11.7 mcg/mL, and the mean C_{min} was 3.4 mcg/mL. The average percent fraction of fluctuation was 244%. The mean T_{max} was 8.7 hours.

The subjects used in the above study exhibited a mean half-life of 7.9 hours (range 5.3-13.4) and a mean clearance of 3.5 L/hour (range 2.3-5.7)

Distribution: Once Theophylline enters the systemic circulation, about 40% is bound to plasma protein, primarily albumin. Unbound theophylline distributes throughout body water, but distributes poorly into body fat. The apparent volume of distribution of theophylline is approximately 0.45 L/kg (range 0.2-0.7 L/kg) based on ideal body weight. Theophylline passes freely across the placenta, into breast milk and into the cerebrospinal fluid (CSF). Saliva theophylline concentrations

approximate unbound serum concentrations, but are not reliable for routine or therapeutic monitoring unless special techniques are used. An increase in the volume of distribution of theophylline, primarily due to reduction in plasma protein binding, occurs in premature neonates, patients with hepatic cirrhosis, uncorrected acidemia, the elderly and in women during the third trimester of pregnancy. In such cases, the patient may show signs of toxicity at total (bound + unbound) serum concentrations of theophylline in the therapeutic range (10-20 mcg/mL) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a sub-therapeutic total drug concentration while the pharmacologically active unbound concentration is in the therapeutic range. If only total serum theophylline concentration is measured, this may lead to an unnecessary and potentially dangerous dose increase. In patients with reduced protein binding, measurement of unbound serum theophylline concentration provides a more reliable means of dosage adjustment than measurement of total serum theophylline concentration. Generally, concentrations of unbound theophylline should be maintained in the range of 6-12 mcg/mL.

Metabolism: Following oral dosing, theophylline does not undergo any measurable first-pass elimination. In adults and children beyond one year of age, approximately 90% of the dose is metabolized in the liver. Biotransformation takes place through demethylation to 1-methylxanthine and 3-methylxanthine and hydroxylation to 1,3-dimethylxanthine. 1-methylxanthine is further hydroxylated, by xanthine oxidase, to 1-methyluric acid. About 6% of a theophylline dose is N-methylated to caffeine. Theophylline demethylation to 3-methylxanthine is catalyzed by cytochrome P-450 1A2, while cytochromes P-450 2E1 and P-450 3A4 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P-450 1A2 or a closely related cytochrome. In neonates, the N-demethylation pathway is absent while the function of the hydroxylation pathway is markedly deficient. The activity of these pathways slowly increases to maximal levels by one year of age.

Caffeine and 3-methylxanthine are the only theophylline metabolites with pharmacologic activity. 3-methylxanthine has approximately one tenth the pharmacologic activity of theophylline and serum concentrations in adults with normal renal function are <1 mcg/mL. In patients with end-stage renal disease, 3-methylxanthine may accumulate to concentrations that approximate the unmetabolized theophylline concentration. Caffeine concentrations are usually undetectable in adults regardless of renal function. In neonates, caffeine may accumulate to concentrations that approximate the unmetabolized theophylline concentration and thus, exert a pharmacologic effect.

Both the N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, non-linearly of elimination may begin in some patients at serum theophylline concentrations >10 mcg/mL. Since this non-linearity results in more than proportional changes in serum theophylline concentrations with changes in dose, it is advisable to make increases or decreases in dose in small increments in order to achieve desired changes in serum theophylline concentrations (see **DOSEAGE AND ADMINISTRATION, Table VI**). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (i.e., low steady-state serum theophylline concentrations at above average doses) have the greatest likelihood of experiencing large changes in serum theophylline concentration in response to dosage changes.

Excretion: In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first three months of age, approximately 10% of the theophylline dose is excreted unchanged in the urine. The remainder is excreted in the urine mainly as 1,3-dimethyluric acid (35-40%), 1-methyluric acid (20-25%) and 3-methylxanthine (15-20%). Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (i.e., caffeine, 3-methylxanthine) 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 theophylline and caffeine in neonates requires careful attention to dose reduction and frequent monitoring of serum theophylline concentrations in neonates with reduced renal function (see **WARNINGS**).

Serum Concentrations at Steady-State: After multiple doses of theophylline, steady-state is reached in 30-65 hours (average 40 hours) in adults. At steady-state, on a dosage regimen with 6-hour intervals, the expected mean trough concentration is approximately 50% of the mean peak concentration, assuming a mean theophylline half-life of 8 hours. The difference between peak and trough concentrations is larger in patients with more rapid theophylline clearance. In patients with high theophylline clearance and half-lives of about 4-5 hours, such as children age 1 to 9 years, the trough serum theophylline concentration may be only 30% of peak with a 6-hour dosing interval. In these patients a slow-release formulation would allow a longer dosing interval (8-12 hours) with a smaller peak/trough difference.

Special Populations (See Table I for mean clearance and half-life values):

Geriatric: The clearance of theophylline is decreased by a mean 30% in healthy elderly adults (> 60 yrs) compared to healthy young adults. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in elderly patients (see **WARNINGS**).

Pediatric: The clearance of theophylline is very low in neonates (see **WARNINGS**). Theophylline clearance reaches maximal values by one year of age, remains relatively constant until about 9 years of age and then slowly decreases by approximately 50% to adult values at about age 16. Renal excretion of unchanged theophylline in neonates amounts to about 50% of the dose, compared to about 10% in children 10% older than three months of age. Careful attention to dosing and close monitoring of serum theophylline concentrations are required in pediatric patients (see **WARNINGS** and **DOSEAGE AND ADMINISTRATION**).

Gender: Gender differences in theophylline clearance are relatively small and unlikely to be of clinical significance. Significant reduction in theophylline clearance, however, has been reported in women on the 20th day of the menstrual cycle and during the third trimester of pregnancy.

Race: Pharmacokinetic differences in theophylline clearance due to race have not been studied.

Renal Insufficiency: Only a small fraction, e.g., about 10%, of the administered theophylline dose is excreted unchanged in the urine of children younger than three months of age. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (i.e., caffeine, 3-methylxanthine) 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, approximately 50% of the administered theophylline dose is excreted unchanged in the urine in neonates. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in neonates with decreased renal function (see **WARNINGS**).

Hepatic Insufficiency: Theophylline clearance is decreased by 50% or more in patients with hepatic insufficiency (e.g., cirrhosis, acute hepatitis, cholestasis). Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with reduced hepatic function (see **WARNINGS**).

Congestive Heart Failure (CHF): Theophylline clearance is decreased by 50% or more in patients with CHF. The extent of reduction in theophylline clearance in patients with CHF appears to be directly correlated to the severity of the cardiac disease. Since theophylline clearance is independent of liver blood flow, the reduction in clearance appears to be due to impaired hepatocyte function rather than reduced perfusion. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with CHF (see **WARNINGS**).

Smokers: Tobacco and marijuana smoking appears to increase the clearance of theophylline by induction of metabolic pathways. Theophylline clearance has been shown to increase by approximately 50% in young adult tobacco smokers and by approximately 80% in elderly tobacco smokers compared to non-smoking subjects. Passive smoke exposure has also been shown to increase theophylline clearance by up to 50%. Abstinence from tobacco smoking for one week causes a reduction of approximately 40% in theophylline clearance. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients who stop smoking (see **WARNINGS**). Use of nicotine gum has been shown to have no effect on theophylline clearance.

Fever: Fever, regardless of its underlying cause, can decrease the clearance of theophylline. The magnitude and duration of the fever appear to be directly correlated to the degree of decrease of theophylline clearance. Precise data are lacking, but a temperature of 39°C (102°F) for at least 24 hours is probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (i.e., those who require a dose that is substantially larger than average [e.g., >22 mg/kg/day]) to achieve a therapeutic peak serum theophylline concentration when afebrile) may be at greater risk of toxic effects from decreased clearance during sustained fever. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with sustained fever (see **WARNINGS**).

Miscellaneous: Other factors associated with decreased theophylline clearance include the third trimester of pregnancy, sepsis with multiple organ failure, and hypothyroidism. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with any of these conditions (see **WARNINGS**). Other factors associated with increased theophylline clearance include hyperthyroidism and cystic fibrosis.

Clinical Studies:

In patients with chronic asthma, including patients with severe asthma requiring inhaled corticosteroids or alternate-day oral corticosteroids, many clinical studies have shown that theophylline decreases the frequency and severity of symptoms, including nocturnal exacerbations, and decreases the "as needed" use of inhaled beta-2 agonists. Theophylline has also been shown to reduce the need for short courses of daily oral prednisone to relieve exacerbations of airway obstruction that are unresponsive to bronchodilators in asthmatics.

In patients with chronic obstructive pulmonary disease (COPD), clinical studies have shown that theophylline decreases dyspnea, air trapping, the work of breathing, and improves contractility of diaphragmatic muscles with little or no improvement in pulmonary function measurements.

INDICATIONS AND USAGE:

Theophylline extended-release tablets are 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.

CONTRAINDICATIONS:

Theophylline extended-release tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product.

WARNINGS:

Concurrent Illness:

Theophylline should be used with extreme caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition:

Active peptic ulcer disease

Seizure disorders

Cardiac arrhythmias (not including bradyarrhythmias)

Conditions that Reduce Theophylline Clearance:

There are several readily identifiable causes that reduce theophylline clearance. *If the total daily dose is not appropriately reduced in the presence of these risk factors, severe and potentially fatal theophylline toxicity can occur.* Careful consideration must be given to the benefits and risks of theophylline use and the need for more intensive monitoring of serum theophylline concentrations in patients with the following risk factors:

Age: Neonates (term and premature), Children <1 year, Elderly (>60 years)

Concurrent Diseases: Acute pulmonary edema, congestive heart failure, cor-pulmonale, fever (>102° for 24 hours or more; or lesser temperature elevations for longer periods), reduced renal function in infants <3 months of age, sepsis with multi-organ failure and shock.

Cessation of Smoking

Drug Interactions: Adding a drug that inhibits theophylline metabolism (e.g., cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (e.g., carbamazepine, rifampin). (see **PRECAUTIONS, Drug Interactions, Table II**).

When Signs or Symptoms of Theophylline Toxicity Are Present: Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), additional doses of theophylline should be withheld and a serum theophylline concentration measured immediately. Patients should be instructed not to continue any dosage that causes adverse effects and to withhold subsequent doses until the symptoms have resolved, at which time the healthcare professional may instruct the patient to resume the drug at a lower dosage (see **DOSEAGE AND ADMINISTRATION, Dosing Guidelines, Table VI**).

Dosage Increases: Increases in the dose of theophylline should not be made in response to an acute exacerbation of symptoms of chronic lung disease since theophylline provides little added benefit to inhaled beta2-selective agonists and systemically administered cortico-steroids in this circumstance and increases the risk of adverse effects. A peak steady-state serum theophylline concentration should be measured before increasing the dose in response to persistent chronic symptoms to assess whether an increase in dose is safe. Before increasing the theophylline dose on the basis of a low serum concentration, the healthcare professional should consider whether the blood sample was obtained an appropriate time in relationship to the dose and whether the patient has adhered to the prescribed regimen (see **PRECAUTIONS, Laboratory Tests**).

As the rate of theophylline clearance may be dose-dependent (i.e., steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a sub-therapeutic serum concentration measurement should be conservative. In general, limiting dose increases to about 25% of the previous total daily dose will reduce the risk of unintended excessive increases in serum theophylline concentration (see **DOSEAGE AND ADMINISTRATION, Table VI**).

PRECAUTIONS:

General:

Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy, prior to increases in theophylline dose, and during follow up (see **WARNINGS**). The dose of theophylline selected for initiation of therapy should be low and, *if tolerated*, increased slowly over a period of a week or longer with the final dose guided by monitoring serum theophylline concentrations and the patient's clinical response (see **DOSEAGE AND ADMINISTRATION, Table V**).

Monitoring Serum Theophylline Concentrations:

Serum theophylline concentration measurements are readily available and should be used to determine whether the dosage is appropriate. Specifically, the serum theophylline concentration should be measured as follows:

- When initiating therapy to guide final dosage adjustment after titration.
- Before making a dosage increase to determine whether the serum concentration is sub-therapeutic in 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 a change in the patient's treatment regimen that may alter theophylline clearance (e.g., fever >102°F sustained for ≥24 hours, hepatitis, or drugs listed in Table II are added or discontinued).

To guide a dose increase, the blood sample should be obtained at the time of the expected peak serum theophylline concentration; 12 hours after an evening dose or 9 hours after a morning dose at steady-state will be reached after 3 days of dosing when no doses have been missed, no extra doses have been added, and none of the doses have been taken at unequal intervals. Before making a dosage increase to determine whether the serum concentration is sub-therapeutic in a patient who continues to be symptomatic, the timing of the dosing interval provides no additional useful information and may lead to an inappropriate dose increase since the peak serum theophylline concentration with an immediate-release formulation. If the serum sample is drawn more than 12 hours after the evening dose, or more than 9 hours after a morning dose, the results must be interpreted with caution since the concentration may not be reflective of the peak concentration. In contrast, when signs or symptoms of theophylline toxicity are present, a serum sample should be obtained as soon as possible, analyzed immediately, and the result reported to the healthcare professional without delay. In patients in whom decreased serum protein binding is suspected (e.g., cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6-12 mcg/mL.

Saliva concentrations of theophylline cannot be used reliably to adjust dosage without special techniques.

Effects on Laboratory Tests:

As a result of its pharmacological effects, theophylline at serum concentrations within the 10-20 mcg/mL range modestly increases plasma glucose (from a mean of 88 mg% to 85 mg%), uric acid (from a mean of 4 mg/dL to 6 mg/dL), free fatty acids (from a mean of 451 μM/L to 800 μM/L, total cholesterol (from a mean of 140 to 160 mg/dL), HDL (from a mean of 36 to 50 mg/dL), HDL/LDL ratio (from a mean of 0.5 to 0.7), and urinary free cortisol excretion (from a mean of 44 to 63 mcg/24 hr). Theophylline at serum concentrations within the 10-20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after one week and 142 ng/dl after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

Information for Patients:

The patient (or parent/care giver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia or rapid heart beat occurs during treatment with theophylline, even if another cause is suspected. The patient should be instructed to contact their healthcare professional if they develop a new illness, especially if accompanied by a persistent fever, if the patient is unable to perform any of their usual activities of daily living, if the patient is taking any other healthcare professional advice on a new medication or discontinues a previously prescribed medication. Patients should be informed that theophylline interacts with a wide variety of drugs (see Table II). The dietary supplement St. John's Wort (Hypericum perforatum) should not be taken at the same time as theophylline, since it may result in decreased theophylline levels. If patients are already taking St. John's Wort and theophylline together, they should consult their healthcare professional before stopping the St. John's Wort, since their theophylline concentrations may rise when this is done, resulting in toxicity. Patients should be instructed to inform all healthcare professional involved in their care that they are taking theophylline, especially when medication is being added or deleted from their treatment. Patients should be instructed to not alter the dose, timing of the dose, or frequency of administration without first consulting their healthcare professional. If a dose is missed, the patient should be instructed to take the next dose at the usually scheduled time and to not attempt to make up for the missed dose.

Theophylline tablets can be taken once a day in the morning or evening. It is recommended that theophylline tablets be taken with meals. Patients should be advised that if they choose to take theophylline tablets with food it should be taken consistently with food and if they take it in a fasted condition it should routinely be taken fasted. It is important that the product whenever dosed be dosed consistently with or without food.

Theophylline Tablets are not to be chewed or crushed because it may lead to a rapid release of theophylline with the potential for toxicity. The scored tablet may be split. Patients receiving theophylline tablets may pass an intact matrix tablet in the stool or via colostomy. These matrix tablets usually contain little or no residual theophylline.

Drug Interactions:

Drug-Drug Interactions: Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, i.e., alterations in the therapeutic response to theophylline or another drug or occurrence of adverse effects, without a change in serum theophylline concentration, or pharmacokinetic, where the interaction is pharmacokinetic, i.e., the rate of theophylline clearance is altered by another drug resulting in increased or decreased serum theophylline concentrations. Theophylline only rarely alters the pharmacokinetics of other drugs.

The drugs listed in Table II have the potential to produce clinically significant pharmacodynamic or pharmacokinetic interactions with theophylline. The information in the "Effect" column of Table II assumes that the interacting drug is being added to a steady-state theophylline regimen. If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (e.g., cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller. Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (e.g., rifampin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

The drugs listed in Table III have either been documented not to interact with theophylline or do not produce a clinically significant interaction (i.e., <15% change in theophylline clearance).

(Study #2 - Sessler, Am J Med 1990;88:567-76), data were retrospectively collected from 116 cases with serum theophylline concentrations >30 mcg/mL among 6000 blood samples obtained for measurement of serum theophylline concentrations in three emergency departments. Differences in the incidence of manifestations of theophylline toxicity between the two studies may reflect sample selection as a result of study design (e.g., in Study #1, 48% of the patients had acute intoxications versus only 10% in Study #2) and different methods of reporting results.

** NR = Not reported in a comparable manner.

OVERDOSAGE:

Generat: The chronicity and pattern of theophylline overdose significantly influences clinical manifestations of toxicity, management and outcome. There are two common presentations: (1) ***acute overdose***, i.e., ingestion of a single large excessive dose (>10 mg/kg) as occurs in the context of an attempted suicide or isolated medication error, and (2) ***chronic overdose***, i.e., ingestion of repeated doses that are excessive for the patient’s rate of theophylline clearance. The most common causes of chronic theophylline overdose include patient or care giver error in dosing, healthcare professional prescribing of an excessive dose or a normal dose in the presence of factors known to decrease the rate of theophylline clearance, and increasing the dose in response to an exacerbation of symptoms without first measuring the serum theophylline concentration to determine whether a dose increase is safe.

Severe toxicity from theophylline overdose is a relatively rare event. In one health maintenance organization, the frequency of hospital admissions for chronic overdose of theophylline was about 1 per 1000 person-years exposure. In another study, among 6000 blood samples obtained for measurement of serum theophylline concentration, for any reason, from patients treated in an emergency department, 7% were in the 20-30 mcg/mL range and 3% were >30 mcg/mL. Approximately two-thirds of the patients with serum theophylline concentrations in the 20-30 mcg/mL range had one or more manifestations of toxicity while >90% of patients with serum theophylline concentrations >30 mcg/mL were clinically intoxicated. Similarly, in other reports, serious toxicity from theophylline is seen principally at serum concentrations >30 mcg/mL.

Several studies have described the clinical manifestations of theophylline overdose and attempted to determine the factors that predict life-threatening toxicity. In general, patients who experience an acute overdose are less likely to experience seizures than patients who have experienced a chronic overdose, unless the peak serum theophylline concentration is >100 mcg/mL. After a chronic overdose, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >30 mcg/mL. The severity of toxicity after chronic overdose is more strongly correlated with the patient’s age than the peak serum theophylline concentration: patients <60 years are at the greatest risk for severe toxicity and mortality after a chronic overdose. Preexisting or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, e.g., patients with neurologic disorders have an increased risk of seizures and patients with cardiac disease have an increased risk of cardiac arrhythmias for a given serum theophylline concentration compared to patients without the underlying disease. The frequency of various reported manifestations of theophylline overdose according to the mode of overdose are listed in Table IV.

Other manifestations of theophylline toxicity include increases in serum calcium, creatine kinase, myoglobin and leukocyte count, decreases in serum phosphate and magnesium, acute myocardial infarction, and urinary retention in men with obstructive uropathy.

Seizures associated with serum theophylline concentrations >30 mcg/mL are often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death from theophylline toxicity is most often secondary to cardiorespiratory arrest and/or hypoxic encephalopathy following prolonged generalized seizures or intractable cardiac arrhythmias causing hemodynamic compromise.

Overdose Management

General Recommendations for Patients with Symptoms of Theophylline Overdose or Serum Theophylline Concentrations >30 mcg/mL (Note: Serum theophylline concentrations may continue to increase after presentation of the patient for medical care.)

- While simultaneously instituting treatment, contact a regional poison center to obtain updated information and advice on individualizing the recommendations that follow.
- Institute supportive care, including establishment of intravenous access, maintenance of the airway, and electrocardiographic monitoring.
- 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 intravenous benzodiazepine (e.g., diazepam, in increments 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). Case reports of theophylline overdose in humans and animal studies suggest that phenytoin is ineffective in terminating theophylline-induced seizures. The doses of benzodiazepines and phenobarbital required to terminate theophylline-induced seizures are close to the doses that may cause severe respiratory depression or respiratory arrest: the healthcare professional should therefore be prepared to provide assisted ventilation. Elderly patients and patients with COPD may be more susceptible to the respiratory depressive effects of anticonvulsants. Barbiturate-induced coma or administration of general anesthesia may be required to terminate repetitive seizures or status epilepticus. General anesthesia should be used with caution in patients with theophylline overdose because fluorinated volatile anesthetics may sensitize the myocardium to endogenous catecholamines released by theophylline. Enflurane appears less likely to be associated with this effect than halothane and may, therefore, be safer. Neuromuscular blocking agents alone should not be used to terminate seizures since they abolish the musculoskeletal manifestations without terminating seizure activity in the brain.
- Anticipate need for anticonvulsants:** In patients with theophylline overdose who are at high risk for theophylline-induced seizures, e.g., patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdose in patients <60 years of age with serum theophylline concentrations >30 mcg/mL, the need for anticonvulsant therapy should be anticipated. A benzodiazepine such as diazepam should be drawn into a syringe and kept at the patient’s bedside and medical personnel qualified to treat seizures should be immediately available. In selected patients at high risk for theophylline-induced seizures, consideration should be given to the administration of prophylactic anticonvulsant therapy. Situations where prophylactic anticonvulsant therapy should be considered in high risk patients include anticipated delays in instituting methods for extracorporeal removal of theophylline (e.g., transfer of a high risk patient from one health care facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (e.g., a neonate where dialysis may not be technically feasible or a patient with vomiting unresponsive to antiemetics who is unable to tolerate multiple-dose oral activated charcoal). In animal studies, prophylactic administration of phenobarbital, *but not phenytoin*, has been shown to delay the onset of theophylline-induced generalized seizures and to increase the dose of theophylline required to induce seizures (i.e., markedly increases the LD₅₀). Although there are no controlled studies in humans, a loading dose of intravenous phenobarbital (20 mg/kg infused over 60 minutes) may delay or prevent life-threatening seizures in high risk patients while efforts to enhance theophylline clearance are continued. Phenobarbital may cause respiratory depression, particularly in elderly patients and patients with COPD.
- Treatment of cardiac arrhythmias:** Sinus tachycardia and simple ventricular premature beats are not harbingers of life-threatening arrhythmias, they do not require treatment in the absence of hemodynamic compromise, 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 arrhythmia.
- 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 gastrointestinal tract, even when administered several hours after ingestion. If the patient is vomiting, the charcoal should be administered through a nasogastric tube or after administration of an antiemetic. Phenothiazine antiemetics such as prochlorperazine or perphenazine should be avoided since they can lower the seizure threshold and frequently cause dystonic reactions. A single dose of sorbitol may be used to promote stooling to facilitate removal of theophylline bound to charcoal from the gastrointestinal tract. Sorbitol, however, should be dosed with caution since it is a potent purgative which can cause profound fluid and electrolyte abnormalities, particularly after multiple doses. Commercially available fixed combinations of liquid charcoal and sorbitol should be avoided in young children and after the first dose in adolescents and adults since they do not allow for individualization of charcoal and sorbitol dosing. Ipecac syrup should be avoided in theophylline overdoses. Although ipecac induces emesis, it does not reduce the absorption of theophylline unless administered within 5 minutes of ingestion and even then is less effective than oral activated charcoal. Moreover, ipecac induced emesis may persist for several hours after a single dose and significantly decrease the retention and the effectiveness of oral activated charcoal.
- Serum theophylline concentration monitoring:** The serum theophylline concentration should be measured immediately upon presentation, 2-4 hours later, and then at sufficient intervals, e.g., every 4 hours, to guide treatment decisions and to assess the effectiveness of therapy. Serum theophylline concentrations may continue to increase after presentation of the patient for medical care as a result of continued absorption of theophylline from the gastrointestinal tract. Serial monitoring of serum theophylline serum concentrations should be continued until it is clear that the concentration is no longer rising and has returned to non-toxic levels.

- General monitoring procedures:** Electrocardiographic monitoring should be initiated on presentation and continued until the serum theophylline level has returned to a non-toxic level. Serum electrolytes and glucose should be measured on presentation and at appropriate intervals indicated by clinical circumstances. Fluid and electrolyte abnormalities should be promptly corrected. **Monitoring and treatment should be continued until the serum concentration decreases below 20 mcg/mL.**
- Enhance clearance of theophylline:** Multiple-dose oral activated charcoal (e.g., 0.5 mg/kg up to 20 g, every two hours) increases the clearance of theophylline at least twofold by absorption of theophylline secreted into gastrointestinal fluids. Charcoal must be retained in, and pass through, the gastrointestinal tract to be effective; emesis should therefore be controlled by administration of appropriate antiemetics. Alternatively, the charcoal can be administered continuously through a nasogastric tube in conjunction with appropriate antiemetics. A single dose of sorbitol may be administered with the activated charcoal to promote stooling to facilitate clearance of the adsorbed theophylline from the gastrointestinal tract. Sorbitol alone does not enhance clearance of theophylline and should be dosed with caution to prevent excessive stooling which can result in severe fluid and electrolyte imbalances. Commercially available fixed combinations of liquid charcoal and sorbitol should be avoided in young children and after the first dose in adolescents and adults since they do not allow for individualization of charcoal and sorbitol dosing. In patients with intractable vomiting, extracorporeal methods of theophylline removal should be instituted (see **OVERDOSAGE, Extracorporeal Removal**).

Specific Recommendations:

Acute Overdose

- Serum Concentration >20-30 mcg/mL**
 - Administer a single dose of oral activated charcoal.
 - Monitor the patient and obtain a serum theophylline concentration in 2-4 hours to insure that the concentration is not increasing.
- Serum Concentration >30-100 mcg/mL**
 - Administer multiple-dose oral activated charcoal and measures to control emesis.
 - Monitor the patient and obtain serial theophylline concentrations every 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.
 - Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be adequately controlled (see **OVERDOSAGE, Extracorporeal Removal**).
- Serum Concentration >100 mcg/mL**
 - Consider prophylactic anticonvulsant therapy.
 - Administer multiple-dose oral activated charcoal and measures to control emesis.
 - Consider extracorporeal removal, even if the patient has not experienced a seizure (see **OVERDOSAGE, Extracorporeal Removal**).
 - Monitor the patient and obtain serial theophylline concentrations every 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Chronic Overdoseage

- Serum Concentration >20-30 mcg/mL (with manifestations of theophylline toxicity)**
 - Administer a single dose of oral activated charcoal.
 - Monitor the patient and obtain a serum theophylline concentration in 2-4 hours to insure that the concentration is not increasing.
- Serum Concentration >30 mcg/mL in patients <60 years of age**
 - Administer multiple-dose oral activated charcoal and measures to control emesis.
 - Monitor the patient and obtain serial theophylline concentrations every 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.
 - Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be adequately controlled (see **OVERDOSAGE, Extracorporeal Removal**).
- Serum Concentration >30 mcg/mL in patients >60 years of age.**
 - Consider prophylactic anticonvulsant therapy.
 - Administer multiple-dose oral activated charcoal and measures to control emesis.
 - Consider extracorporeal removal even if the patient has not experienced a seizure (see **OVERDOSAGE, Extracorporeal Removal**).
 - Monitor the patient and obtain serial theophylline concentrations every 2-4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Extracorporeal Removal:

Increasing the rate of theophylline clearance by extracorporeal methods may rapidly decrease serum concentrations, but the risks of the procedure must be weighed against the potential benefit. Charcoal hemoperfusion is the most effective method

of extracorporeal removal, increasing theophylline clearance up to sixfold, but serious complications, including hypotension, hypocalcemia, platelet consumption and bleeding diatheses may occur. Hemodialysis is about as efficient as multiple-dose oral activated charcoal and has a lower risk of serious complications than charcoal hemoperfusion. Hemodialysis should be considered as an alternative when charcoal hemoperfusion is not feasible and multiple-dose oral charcoal is ineffective because of intractable emesis. Serum theophylline concentrations may rebound 5-10 mcg/mL after discontinuation of charcoal hemoperfusion or hemodialysis due to redistribution of theophylline from the tissue compartment. Peritoneal dialysis is ineffective for theophylline removal; exchange transfusions in neonates have been minimally effective.

DOSSAGE AND ADMINISTRATION:

Taking theophylline extended-release tablets immediately after a high-fat content meal may result in a somewhat higher C_{max} and delayed T_{max} and somewhat greater extent of absorption. However, the differences are usually not great and this product may normally be administered without regard to meals (see **CLINICAL PHARMACOLOGY, Drug Interactions, Drug-Food Interactions**).

Theophylline extended-release tablets are recommended for chronic or long-term management and prevention of symptoms, and not for use in treating acute symptoms of asthma and reversible bronchospasm.

General considerations:

The steady-state peak serum theophylline concentration is a function of the dose, the dosing interval, and the rate of theophylline absorption and clearance in the individual patient. Because of marked individual differences in the rate of theophylline clearance, the dose required to achieve a peak serum theophylline concentration in the 10-20 mcg/mL range varies fourfold among otherwise similar patients in the absence of factors known to alter theophylline clearance (e.g., 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 years old). For a given population there is no single theophylline dose that will provide both safe and effective serum concentrations for all patients. Administration of the median theophylline dose required to achieve a therapeutic serum theophylline concentration in a given population may result in either sub-therapeutic or potentially toxic serum theophylline concentrations in individual patients. For example, at a dose of 900 mg/d in adults <60 years or 22 mg/kg/d in children 1-9 years, the steady-state peak serum theophylline concentration will be <10 mcg/mL in about 30% of patients, 10-20 mcg/mL in about 50% and 20-30 mcg/mL in about 20% of patients. **The dose of theophylline must be individualized on the basis of peak serum theophylline concentration measurements in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.**

Transient caffeine-like adverse effects and excessive serum concentrations in slow metabolizers can be avoided in most patients by starting with a sufficiently low dose and slowly increasing the dose, *if judged to be clinically indicated*, in small increments (see Table V). Dose increases should only be made if the previous dosage is well tolerated and at intervals of no less than 3 days to allow serum theophylline concentrations to reach the new steady state. Dosage adjustment should be guided by serum theophylline concentration measurement (see **PRECAUTIONS, Laboratory Tests and DOSSAGE AND ADMINISTRATION, Table IV**). Health care providers should instruct patients and care givers to discontinue any dosage that causes adverse effects, to withhold the medication until these symptoms are gone and to then resume therapy at a lower, previously tolerated dosage (see **WARNINGS**).

If the patient’s symptoms are well controlled, there are no apparent adverse effects, and no intervening factors that might alter dosage requirements (see **WARNINGS and PRECAUTIONS**), serum theophylline concentrations should be monitored at 6 month intervals for rapidly growing children and at yearly intervals for all others. In acutely ill patients, serum theophylline concentrations should be monitored at frequent intervals, e.g., every 24 hours.

Theophylline distributes poorly into body fat, therefore, mg/kg dose should be calculated on the basis of ideal body weight.

Table V contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. Table VI contains recommendations for theophylline dosage adjustment based upon serum theophylline concentrations. **Application of these general dosing recommendations to individual patients must take into account the unique clinical characteristics of each patient. In general, these recommendations should serve as the upper limit for dosage adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

Table V. Dosing initiation and titration (as anhydrous theophylline)*

A. Children (6-15 years) and adults (16-60 years) without risk factors for impaired clearance.

Titration Step	Children <45 kg	Children >45 kg and adults
1 Starting Dosage	12-14 mg/kg/day up to a maximum of 300 mg/day divided Q12 hrs*	300 mg/day divided Q12 hrs*
2 After 3 days, <i>if tolerated</i> , increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day divided Q12 hrs*	400 mg/day divided Q12 hrs*
3 After 3 more days, <i>if tolerated</i> , increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day divided Q12 hrs*	600 mg/day divided Q12 hrs*

B. Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:

In children 6-15 years of age, the final theophylline dose should not exceed 16 mg/kg/day up to a maximum of 400 mg/day in the presence of risk factors for reduced theophylline clearance (see **WARNINGS**) or if it is not feasible to monitor serum theophylline concentrations. In adolescents >16 years and adults, including the elderly, the final theophylline dose should not exceed 400 mg/day in the presence of risk factors for reduced theophylline clearance (see **WARNINGS**) or if it is not feasible to monitor serum theophylline concentrations.

- Patients with more rapid metabolism, clinically identified by higher than average dose requirements, should receive a smaller dose more frequently (every 8 hours) to prevent breakthrough symptoms resulting from low trough concentrations before the next dose.

Table VI. Dosage adjustment guided by serum theophylline concentration.

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after three days for further dosage adjustment.
10 to 14.9 mcg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6-12 month intervals † If symptoms are not controlled and current dosage is tolerated consider adding additional medication(s) to treatment regimen.
15-19.9 mcg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated. †
20-24.9 mcg/mL	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment.
25-30 mcg/mL	Skip next dose and decrease subsequent doses at least 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated (see recommendations for chronic overdose).
>30 mcg/mL	Treat overdose as indicated (see recommendations for chronic overdose). If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 days to guide further dosage adjustment.

† Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiologic abnormalities that can reduce theophylline clearance occur (e.g