BRONCHODILATORS, THEOPHYLLINE (Systemic)
Aminophylline

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Asthma, bronchial (prophylaxis and treatment)¾ Aminophylline, oxtriphylline, and theophylline are indicated for the prevention and treatment of bronchial asthma symptoms. They improve pulmonary function and reduce the frequency and severity of symptoms such as wheezing, cough, shortness of breath, or dyspnea. 2, 153

Some studies have shown that theophylline does not provide additional benefit in the initial treatment of acute airway obstruction when optimal therapy is provided with inhaled or injected beta-2-adrenergic bronchodilators and systemic glucocorticoids in patients not already receiving a methylxanthine. 3, 4, 13, 14, 15, 16, 49 Although patients hospitalized with asthma may benefit from administration of aminophylline or theophylline, these medications should not be relied upon to produce immediate bronchodilation, even if therapeutic theophylline concentrations are rapidly achieved. 17, 49

Aminophylline, oxtriphylline, and theophylline may benefit those patients with an inadequate response to anti-inflammatory medications and beta-adrenergic bronchodilators; however, theophylline bronchodilators are not considered to be first-line therapy. 49, 163

Bronchitis, chronic (treatment)

Emphysema, pulmonary (treatment) or

Pulmonary disease, chronic obstructive, other (treatment)¾Aminophylline, oxtriphylline, and theophylline may be indicated in the treatment of reversible airway obstruction associated with chronic bronchitis, emphysema, or other chronic obstructive pulmonary disease. 18, 19, 20, 21, 22, 23, 153

[Apnea, neonatal (treatment adjunct)] *¾Aminophylline oral solution and injection and theophylline oral liquids are used in the treatment of idiopathic apnea in neonates, characterized by cessation of respiration that lasts 20 seconds or longer. 25, 26, 27, 156 Aminophylline or theophylline should be considered in addition to administration of oxygen, sensory stimulation, or low pressure nasal continuous positive airway pressure. 24

Toxicity, dipyridamole (treatment) *¾Parenteral aminophylline is used to reverse the adenosine-mediated adverse effects of dipyridamole, such as angina pectoris, ventricular arrhythmias, bronchospasm, and severe hypotension. 123

Unaccepted

Parenteral aminophylline and theophylline have been used in the treatment of Cheyne-Stokes respiration. However, there is insufficient evidence to establish the efficacy of these medications for this indication. 157

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Source¾Aminophylline: Theophylline compound with ethylenediamine 70

Oxtriphylline: The choline salt of theophylline 70

Molecular weight¾Aminophylline: 420.43 70

Oxtriphylline: 283.33 70

Theophylline: 198.18 70

Mechanism of action/Effect:

The exact mechanism of action by which theophylline produces its pharmacologic effect is unknown; it is likely to involve multiple mechanisms. 28

Bronchodilator; asthma prophylactic¾Theophylline directly relaxes smooth muscle in the bronchial airways and pulmonary blood vessels. This action is believed to be mediated by selective inhibition of specific phosphodiesterases (PDEs), which in turn produces an increase in intracellular cyclic 3¢, 5¢-adenosine monophosphate (cyclic AMP). 28, 29 In vitro study results demonstrate that the PDE isoenzyme types III and IV may play a primary role. Inhibition of these isoenzymes may also mediate certain theophylline side effects such as emesis, hypotension, and tachycardia. Theophylline also demonstrates adenosine receptor antagonism, which may contribute to its effect on bronchial airways. 28, 176

Respiratory stimulant¾Theophylline is believed to stimulate the medullary respiratory center, presumably by increasing sensitivity to the stimulatory actions of carbon dioxide. 69

Antidote (to dipyridamole toxicity)¾Involves antagonism of the coronary vasodilatory effects of the increased concentrations of adenosine produced by intravenous administration of dipyridamole during myocardial perfusion studies. 123

Other actions/effects:

Theophylline may attenuate airway hyperreactivity associated with the late phase response that is induced by inhaled allergens by an undefined mechanism which is not attributable to PDE inhibition or adenosine antagonism. 1, 29, 30, 33 Theophylline also has been reported to increase the number and activity of suppressor T-cells in the peripheral blood. 31, 32 Whether these actions are clinically relevant is not clear.

Theophylline may produce other physiologic effects such as transient diuresis, stimulation of cardiac muscle, improved contractility of the diaphragm, reduction of systemic and pulmonary vascular resistance, increased gastric acid secretion, central nervous system stimulation, and cerebral vasoconstriction. 69

Absorption:

Immediate-release capsule, liquid, or tablet dosage forms¾Rapidly and completely absorbed. The rate of absorption may be slowed by concurrent ingestion of food or magnesium-containing antacids; however, the effect on the extent of absorption is generally not clinically significant. 1, 5

Delayed-release tablets¾Enteric coating provides delayed and possibly incomplete absorption compared with immediate-release dosage forms. 5, 34

Extended-release capsules or tablets¾The rate of absorption varies among different formulations and is slower than with immediate-release products; the extent of absorption may also vary. Significant intra- and interindividual differences in absorption have been reported. 6, 35 Serum concentration fluctuations are most apparent in patients demonstrating increased theophylline clearance. Co-administration of antacids or food may only slow the rate of absorption from some extended-release formulations, while significantly altering the extent of absorption from others. Some formulations designed for once-a-day administration may be substantially affected by food. 1, 6

Intramuscular¾Slow absorption; medication may precipitate at the injection site. 5

Suppository¾Slow and unreliable absorption. 5, 7

Distribution:

Theophylline distributes rapidly into peripheral non-adipose tissues and body water, including breast milk and cerebrospinal fluid. It freely crosses the placenta. 2, 5 The apparent volume of distribution (Vol D) for theophylline averages 0.45 L per kg of body weight (L/kg) and ranges from 0.3 to 0.7 L/kg (30 to 70% of ideal body weight) in both adults and children. The Vol D may be increased, probably due to altered protein binding 1, 5 , in premature neonates, adults with cirrhosis, patients with uncorrected acidemia, elderly patients, 5 pregnant women during the third trimester, 35 critically ill patients, mechanically ventilated adults, and children with protein-calorie malnutrition. 1

Protein binding:

Moderate (40%). Primarily to albumin 1.

Patients with reduced protein binding may have low total serum theophylline concentrations when unbound theophylline is in the therapeutic range. 153

Biotransformation:

Aminophylline and oxtriphylline¾ Release free theophylline at physiologic pH 69, 177.

Theophylline¾ Hepatic; no first-pass effect. 1 Believed to occur over multiple parallel pathways, mediated by cytochrome P-450 isoenzymes P-4501A2, P-4503A3, and P-4502E1. 41 In neonates, several of these pathways are undeveloped but mature slowly over the first year of life. 42, 43, 44, 45 Caffeine is a minor active metabolite, except in premature neonates and children less than 6 months of age, in whom caffeine's extremely long half-life results in significant accumulation. The half-life of caffeine shortens over the first 6 months of life because of maturation of its metabolic pathway. Thereafter, caffeine does not accumulate in older children and adults. 42, 44, 63 Major inactive metabolites in adults and children older than 6 months of age are 1,3-dimethyluric acid, 3-methylxanthine, and 1-methyluric acid. 42, 44, 63

Theophylline approximates first-order elimination kinetics, where serum concentrations follow a log-linear decay. However, zero-order kinetics, where elimination becomes dependent on the serum concentration, can be observed in patients at therapeutic concentrations. This is probably due to capacity limitations of the hepatic enzymes that metabolize theophylline, and is clinically relevant for some patients in that a small change in theophylline dosage may result in a disproportionately large change in serum concentration. 1, 6, 177

Half-life:

Elimination half-life and total body clearance values for theophylline in various patients are as follows¾

Patient characteristics	Half-life Mean (Range) a (hr)	Total body clearance Mean (Range) a (mL/kg/min)
Age		
Premature neonates		
3-15 days b	30 (17-43)	0.29 (0.09-0.49)
25-57 days b	20 (9.4-30.6)	0.64 (0.04-1.2)
Term infants	(25-26.5)	
1-2 days b	11 (6-29)	
3-26 weeks b		
Children		
1-4 yrs	3.4 (1.2-5.6)	1.7 (0.5-2.9)
4-12 yrs		1.57 (0.83-2.31)
13-15 yrs		0.88 (0.38-1.38)
6-17 yrs c	3.7 (1.5-5.9)	1.4 (0.2-2.6)
Adults d	8.2 (6.1-12.8)	0.65 (0.27-1.03)
Elderly e	9.8 (1.6-18)	0.41 (0.21-0.61)
Concurrent illness or altered physiologic state		
Acute pulmonary edema	19 (3.1-82) f	0.33 (0.07-2.35) f
COPD g	11 (9.4-12.6)	0.54 (0.44-0.64)
COPD and cor pulmonale		0.48 (0.08-0.88)

Cystic fibrosis h	6 (1.8-10.2)	1.25 (0.31-2.19)
Fever i	7 (1-13)	
Hepatic disease		
Acute hepatitis	19.2 (16.6-21.8)	0.35 (0.25-0.45)
Cholestasis	14.4 (5.7-31.8)	0.65 (0.25-1.45)
Cirrhosis	32 (10-56) f	0.31 (0.1-0.7) f
Hyperthyroidism	4.5 (3.7-5.6)	0.8 (0.68-0.97)
Hypothyroidism	11.6 (8.2-25)	0.38 (0.13-0.57)
Pregnancy		
First trimester	8.5 (3.1-13.9)	
Second trimester	8.8 (3.9-13.8)	
Third trimester	13.3 (8.4-17.6)	
Sepsis j	18.8 (6.3-24.1)	0.46 (0.19-1.9)

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

b Postnatal age.

c Elimination half-life and total body clearance gradually become slower until adult values are reached. 177

d Otherwise healthy, nonsmoking asthmatics.

e Nonsmokers with normal cardiac, liver, and renal function; 70 to 85 years of age.

f Median.

g Stable; older than 60 years of age; at least 1 year since stopped smoking.

h Patients 14 to 28 years of age.

i Associated with acute viral respiratory illness in children 9 to 15 years of age.

j With multi-organ failure.

Time to peak concentration:

Theophylline¾ Immediate-release capsules, tablets, or oral solution: 1 to 2 hours. 6, 7

Delayed-release tablets: Approximately 4 hours. 34

Extended-release capsules and tablets: 4 to 13 hours depending upon the specific product.

Therapeutic serum concentration

Bronchodilator¾ For most patients, a conservative goal of therapy would be to target peak steady-state serum concentrations in the range of 5 to 15 mcg/mL (27.5 to 82.5 micromoles/L). 1, 39, 40, 54, 154 Although improved pulmonary function is evident over the range of 5 to 20 mcg/mL (27.5 to 110 micromoles/L), 36, 37 concentrations at the upper end of the therapeutic range may be associated with an increased potential for toxicity. When serum concentrations exceed 20 mcg/mL (110 micromoles/L), the probability of toxicity increases. 1, 39, 40

Respiratory stimulant¾ Neonatal apnea: Steady-state peak serum concentrations of 5 to 12 mcg per mL (27.5 to 66 micromoles per L). 61, 162

Elimination:

Theophylline¾ Renal; approximately 10% excreted unchanged in the urine in adults; amount excreted unchanged may reach 50% in neonates. 1

In dialysis: Charcoal hemoperfusion increases theophylline clearance 2 to 4 times. Hemodialysis and peritoneal dialysis are estimated to increase theophylline clearance by approximately 50% and 30%, respectively. 1

Precautions to Consider

Carcinogenicity/Tumorigenicity

Long-term studies have not been done in humans. The results of long-term carcinogenicity studies performed in mice and rats are pending. 153

Mutagenicity

Theophylline has not been shown to be mutagenic in Ames salmonella, in vivo and in vitro cytogenetics, micronucleus and Chinese hamster ovary test systems. 153

Pregnancy/Reproduction

Fertility¾Studies in rodents have shown that theophylline impairs fertility in mice given oral doses approximately 1 to 3 times the human dose on a mg per square meter of body surface area (mg/m 2), and in rats given oral doses approximately 2 times the human dose on a mg/m 2 basis. 153

Pregnancy¾Although adequate and well-controlled studies in pregnant women have not been done, these medications are used in pregnancy when the risk of treatment is preferable to the risk of placental hypoxemia from uncontrolled pulmonary disease. 46, 47 The Collaborative Perinatal Project monitored 193 mother-child pairs exposed to theophylline during the first trimester and found no evidence of association with teratogenicity. 46

Theophylline crosses the placenta; cord blood concentrations are approximately equal to the maternal serum concentration. 46 Because of this, higher-than-recommended serum concentrations during

pregnancy may result in potentially dangerous serum theophylline and caffeine concentrations in the neonate. Tachycardia 82 , irritability, jitteriness, and vomiting have been reported; therefore, neonates of mothers taking these medications during pregnancy should be monitored for signs of theophylline toxicity. 83

Theophylline clearance is reported to be lower in the third trimester, which may necessitate more frequent theophylline serum concentration determinations and possible dosage reductions. 48

Theophylline was not teratogenic in mice or rats given oral doses approximately 2 and 3 times the recommended human dose on a mg/m 2 basis, respectively. Embryotoxicity was observed in rats given 220 mg per kg of body weight, in the absence of maternal toxicity. 153

FDA Pregnancy Category C. 46

Labor¾Theophylline has been shown to slightly inhibit uterine contractions. 46

Breast-feeding

Less than 1% of a maternal theophylline dose distributes into breast milk; 48 this may cause irritability in the infant. 46

Pediatrics

Caution is recommended in neonates and children less than 1 year of age, especially in premature neonates and in infants less than 3 months of age with renal function impairment, because theophylline clearance is reduced, resulting in lower dosage requirements. Clearance progressively increases over the first year of life, remains constant during the subsequent 9 years, and gradually declines to mean adult values by 16 years of age. 1, 44, 153

Geriatrics

Caution is recommended when aminophylline, oxtriphylline, or theophylline is used in patients older than 60 years of age. 153 Theophylline clearance in healthy adults older than 60 years of age is 30% lower than in healthy younger adults. These patients may require adjustment in dosage or dosing interval. 1, 50, 95, 153 Severe signs or symptoms of toxicity resulting from chronic overdose are more common in elderly patients, occurring in 65% of patients 60 years of age or older with serum theophylline concentrations > 30 mcg per mL (165 micromoles per L). 52

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Pharmacokinetic interactions

Medications that decrease theophylline clearance

(the medications listed in the table below probably decrease theophylline clearance by inhibition of one or more hepatic cytochrome P-450 isoenzyme; changes in clearance of approximately 25% or greater can have clinical significance 106 ; monitoring of serum theophylline concentrations and/or dosage adjustments are strongly recommended when concurrent use of these medications with aminophylline, oxtriphylline, or theophylline is initiated or discontinued

Medication	Decrease in Clearance (avg. %)	Increase in Serum Concentration (avg. %)
a Alcohol b	25	33
Allopurinol c	20	25
>> Cimetidine	33	33-50
Contraceptives, estrogen-containing, oral	25-34	33-50
Disulfiram d	21-33	25-50
Fluoroquinolone antibiotics e		
>> Ciprofloxacin	20-40	25-66
>> Enoxacin	40-70	66-300
>> Fluvoxamine	100	>300
>> Interferon alpha, recombinant	10-50	11-100
Macrolide antibiotics f		
>> Clarithromycin	20	25
>> Erythromycin	5-35	5-50
>> Troleandomycin	25-50 g	33-100
Methotrexate h	15-25	18-33
>> Mexiletine	43	75
Propafenone		40 i
>> Pentoxifylline		30 (0-95)
>> Propranolol	30-50	40-100
>> Tacrine	50	100
>> Thiabendazole	66	>200
>> Ticlopidine	37	60
Verapamil	14-23	16-30

a Calculation based on reported change in clearance if actual change not reported. 147

b 3 mL of whiskey per kg of body weight as a single dose decreased clearance up to 24 hrs.

c ³600 mg per day.

d Dose-dependent, 250 and 500 mg.

e Norfloxacin, lomefloxacin, and ofloxacin are not considered to significantly decrease theophylline clearance. 127

f Azithromycin does not appear to alter theophylline clearance. 115

g Once-daily dose decreases clearance by average of 25%. 132

h Low-dose intramuscular regimen of 15 mg per week.

i Beta-2-antagonist effect may decrease effect of theophylline. 153)

Medications that increase theophylline clearance

(the medications listed in the table below probably increase theophylline clearance by induction of one or more hepatic cytochrome P-450 isoenzyme; changes in clearance of approximately 25% or greater can have clinical significance 106 ; monitoring of serum theophylline concentrations and/or dosage adjustments are strongly recommended when concurrent use of these medications with aminophylline, oxtriphylline, or theophylline is initiated or discontinued

Medication	Increase in Clearance (avg. %)	Decrease in Serum Concentration (avg. %)
a Aminoglutethimide	18-43	15-30
Carbamazepine	33	25
Isoproterenol, intravenous	21	17
>> Moricizine	44-66	30-40
Phenobarbital	33	25
>> Phenytoin	35-75	25-43
>> Rifampin	64-100	40-50

a Calculation based on reported change in clearance if actual change not reported. 150, 151)

Pharmacodynamic or other drug interactions

Adenosine

(concurrent use with theophylline may antagonize the cardiovascular effects of adenosine; larger doses of adenosine may be required or alternative therapy should be used 137)

Benzodiazepines

(theophylline may reverse benzodiazepine sedation; caution is recommended when starting or stopping either medication 114)

>> Beta-adrenergic blocking agents, including ophthalmic agents

(concurrent use with theophylline may result in inhibition of its bronchodilator effect; although agents with beta-1-selectivity may be less antagonistic, extreme caution is recommended if beta-adrenergic blocking agents are used in patients with bronchospasm 109)

Ephedrine

(concurrent use with theophylline may result in increased frequency of nausea, nervousness, or insomnia 5)

>> Halothane

(ventricular arrhythmias have been reported when halothane is used concurrently with theophylline 138)

>> Ketamine

(concurrent use with theophylline may lower the seizure threshold 139)

Lithium

(concurrent use of lithium with theophylline may increase renal elimination of lithium, thus decreasing its therapeutic effect 140)

Neuromuscular blocking agents, nondepolarizing

(concurrent use with theophylline may antagonize neuromuscular blocking effects; a larger dose of neuromuscular blocking agent may be required 141)

>> Smoking tobacco or marijuana

(induces the hepatic metabolism of theophylline, resulting in increased clearance and decreased serum concentrations. 5 Passive smoking may also increase theophylline clearance. Induction is attributed to the polyaromatic hydrocarbons in smoke. Following cessation of cigarette smoking, theophylline clearance begins to decrease after 1 week; 1 however, normalization may require 6 months to 2 years. 71, 84 Dosage adjustments and/or additional theophylline serum determinations may be necessary when smoking is started or stopped)

Sucralfate

(concurrent use with aminophylline, oxtriphylline, or theophylline may result in adsorption of the theophylline bronchodilator if medications are administered less than 2 hours apart 112, 120, 121)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

>> Dipyridamole-assisted myocardial perfusion studies

(the theophylline bronchodilators reverse the effects of dipyridamole on myocardial blood flow, thereby interfering with test results; dipyridamole-assisted myocardial perfusion studies should not be performed if therapy with aminophylline, oxtriphylline, or theophylline cannot be withheld for 36 hours prior to the test 123)

With physiology/laboratory test values 153

Cholesterol and

Free cortisol excretion, urinary and

Free fatty acids and

Glucose, plasma and

HDL and HDL/LDL ratio and

Uric acid, plasma

(concentrations may be increased by theophylline serum concentrations within the therapeutic range)

Triiodothyronine, serum

(concentration may be transiently decreased by theophylline serum concentrations within the therapeutic range)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Acute pulmonary edema or

>> Congestive heart failure or

Fever, sustained or

>> Hepatic disease or

>> Hypothyroidism, not optimally controlled or

>> Sepsis

(theophylline clearance may be decreased, resulting in increased theophylline serum concentrations) (the extent to which fever, as opposed to other complicating factors such as acute viral illness, affects theophylline clearance is controversial 165, 166, 167, 168, 169, 170, 171, 172 ; however, some practitioners recommend additional monitoring and/or dose reduction when the body temperature is 102 °F or greater for at least 24 hours, or when a lower temperature elevation persists for a longer period 153, 173)

Gastritis, active or

Peptic ulcer disease, 71, 76 active

(may be exacerbated because theophylline increases gastric acid secretion)

Gastroesophageal reflux

(theophylline may decrease lower esophageal sphincter pressure, resulting in increased gastroesophageal reflux 122, 158)

>> Seizure disorder 153

(aminophylline, oxtriphylline, or theophylline may lower the seizure threshold; caution is recommended unless the patient is receiving appropriate anticonvulsant therapy 80)

Tachyarrhythmias

(condition may be exacerbated at higher theophylline serum concentrations 5, 71, 76)

>> Sensitivity to a theophylline bronchodilator or ethylenediamine 71, 76, 80

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Caffeine concentrations, serum

(determinations may be required in neonates; usually necessary only if adverse effects occur when the serum theophylline concentration is within the therapeutic range)

Pulmonary function tests

(objective measures of lung function are essential for diagnosis and for guiding therapeutic decision making in asthma; measurement of forced expiratory airflow, using a spirometer or a peak expiratory flowmeter, is recommended at periodic intervals 49)

>> Theophylline concentrations

(dosage requirements are usually guided by measurement of the peak serum concentration obtained at the expected time of the peak, depending upon the specific product characteristics; 5 the frequency of determinations should relate to the specific clinical situation)
(theophylline determinations are recommended when initiating therapy, before increasing the dose when a patient fails to exhibit the expected results, at the appearance of any adverse reaction 49 , whenever any change in physiologic state or medication known to alter theophylline elimination occurs, and upon the addition of any new medication with an unknown effect on theophylline elimination; 61 also recommended at least every 6 to 12 months in stable patients 5)
(blood samples obtained for guidance of therapy should be collected during steady-state conditions, which are generally reached after 48 76, 78 to 72 hours of treatment, provided that the medication is taken at regular intervals, with no missed or extra doses. 71 Steady-state conditions may not be reached for up to 5 days in patients with factors known to decrease theophylline clearance. 5 On each occasion, blood samples should be obtained during the same dosing interval, due to the diurnal variation in the absorption of these medications 5, 51)
(for intravenous therapy, concentrations may be determined 30 to 60 minutes after an intravenous loading dose 177 , approximately 8 to 12 hours after initiating continuous intravenous therapy, and at approximately 24-hour intervals during continuous intravenous therapy 5)
(trough concentration may be useful when evaluating serum concentration-time profiles; determinations may be performed just before the next dose or, for once-daily evening administration of an extended-release product, the morning following a dose 1, 5)
(caution is recommended in interpreting serum theophylline concentrations in patients with low albumin; total serum theophylline concentrations may be low when unbound theophylline is in the therapeutic range; measurement of unbound serum theophylline concentration provides a more reliable basis for dosage adjustment 153, 160)
(caution is recommended in interpreting the results of rapid theophylline immunoassays for uremic patients, because falsely high values may occur. 1 Also, when theophylline concentration is determined via high pressure liquid chromatography, sulfamethoxazole may cause inaccurate test results and large doses of ampicillin, cephalothin, or acetazolamide may cause falsely high concentrations. 8, 83 Determinations via specific immunoassay or high pressure liquid chromatography are not affected by caffeine or dyphylline. 71, 76, 78 However, when theophylline is measured via spectrophotometry, caffeine [including caffeine-containing substances such as chocolate, coffee, tea, colas, or medications] or acetaminophen may cause falsely high concentrations 81)

Note: Concentrations in saliva are approximately 60% of serum concentrations; 2, 5 however, the saliva-to-serum concentration ratio may not remain constant within the same patient 5 ; caution is recommended in use and interpretation of the data without the use of special techniques. 153

Side/Adverse Effects

Note: The less severe signs or symptoms of toxicity, such as continuing or severe abdominal pain, agitation, confusion or change in behavior, diarrhea, hematemesis, hypotension, trembling, and continued vomiting, do not always precede the more serious ones such as sinus tachycardia, ventricular arrhythmias, or seizures 2.

Patients with chronic overdosage have a greater risk for serious toxicity at lower serum concentrations than patients with acute single overdosage. 2, 52 Severe signs or symptoms of toxicity resulting from

chronic overdose are more common in elderly patients, occurring in 65% of patients 60 years of age or older with serum theophylline concentrations > 30 mcg/mL (165 micromoles/L). 52 For additional information about acute or chronic overdose, refer to the Overdose section of this monograph.
Although some studies do not support the suggestion that theophylline has an adverse effect on behavioral and cognitive function in children, 49, 56, 57 differences in individual response have been reported 155, 161 ; monitoring for these effects may be advisable.
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Gastroesophageal reflux 122 (heartburn; vomiting)

Note: Aminophylline, oxtriphylline, or theophylline may relax the gastroesophageal sphincter; however, if vomiting occurs, theophylline toxicity should be considered.

Incidence rare

For aminophylline only

Dermatitis, ethylenediamine hypersensitivity-induced 82 (hives; skin rash; sloughing of skin)

Note: Ethylenediamine hypersensitivity-induced dermatitis can appear up to 48 hours after administration of aminophylline. 82

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Headache 5; increased urination 5; insomnia 5 (trouble in sleeping); nausea 5; nervousness 142; tachycardia 142 (fast heartbeat); trembling 142

Note: These caffeine-like side effects may occur at therapeutic theophylline serum concentrations, especially if the concentrations are rapidly attained. Tolerance generally develops within 1 or 2 weeks; however, the symptoms may persist in < 3% of children and < 10% of adults with chronic therapy 2, 153 despite therapeutic serum theophylline concentrations. 142 Starting therapy at a low dose and slowly increasing the dose by no more than 25% at no less than 3-day intervals until the desired daily dose is reached may prevent the caffeine-like side effects. 5

For parenteral aminophylline and theophylline¾with too rapid intravenous administrationAnxiety 55; headache 55; nausea 55; vomiting 55

Note: Hypotension and cardiac arrest have been reported following rapid direct administration through a central venous catheter. 5

Overdose

For specific information on the agents used in the management of theophylline overdose, see:
- Anesthetics, Inhalation (Systemic) monograph;
- Benzodiazepines (Systemic) monograph;
- Charcoal, Activated (Oral-Local) monograph;
- Metoclopramide (Systemic) monograph;
- Neuromuscular Blocking Agents (Systemic) monograph;
- Ondansetron (Systemic) monograph;
- Phenobarbital in Barbiturates (Systemic) monograph;
- Polyethylene Glycol and Electrolytes (Local)monograph; and/or
- Thiopental in Anesthetics, Barbiturate (Systemic) monograph.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Theophylline is associated with a significant potential for toxicity because of its narrow therapeutic index. The upper limit of the therapeutic serum concentration range is considered to be 20 mcg per mL (mcg/mL) (110 micromoles per L [micromoles/L]). Clinical symptoms of toxicity become evident in some patients with serum concentrations above 15 mcg/mL (82.5 micromoles/L), and increase in frequency when 20 mcg/mL (110 micromoles/L) is exceeded. 53 Less severe toxicities do not always precede major toxicities. Serum theophylline concentrations do not always predict who will experience life-threatening toxicity. Theophylline demonstrates concentration-dependent elimination kinetics as its metabolic pathways become saturated, resulting in prolonged elimination. 1, 6

Theophylline overdose is associated with significant morbidity and mortality, primarily due to the development of arrhythmias or seizures. Patients who develop seizures are at the highest risk for further morbidity and mortality from associated hypoxia, acidosis, rhabdomyolysis, or myoglobinuric renal failure. 64 The type of theophylline overdose has significant influence on clinical outcome. Chronic theophylline overdose appears to be associated with a greater frequency of seizures and arrhythmias at lower theophylline concentrations, when compared with acute overdose outcomes 52, 64 ; this is especially true in patients older than 60 years of age 52.

Although there is a lack of correlation between serum theophylline concentrations and clinical course of a chronic overdose, serum theophylline concentrations > 40 mcg/mL (220 micromoles/L) are considered potentially life-threatening. 64 Following an acute overdose, serum theophylline concentrations of > 90 mcg/mL (495 micromoles/L) are associated with major toxicity, especially seizures. 64 The onset and duration of theophylline toxicity vary and depend on the formulation used, the route of administration, the amount ingested, time since the ingestion, and the patient's theophylline elimination capacity.

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Acute and chronic effects

Abdominal pain, continuing or severe 53; agitation 64 (nervousness or restlessness, continuing); confusion or change in behavior 53; diarrhea 53; hematemesis 53 (dark or bloody vomit); hyperglycemia 64, 83; hypokalemia 64, 83; hypotension 64, 83 (dizziness; lightheadedness); metabolic acidosis 64, 83; seizures 64, 83 (convulsions); tachyarrhythmias 64, 83 (fast and irregular heartbeat); tachycardia 64, 83 (fast heartbeat); trembling, continuing 64, 83; vomiting 64, 83

Treatment of overdose

There is no antidote for theophylline overdose. Treatment is symptomatic and supportive.
To decrease absorption¾ Regardless of the route or mode of exposure resulting in toxicity, oral activated charcoal (OAC) should be administered. 64 OAC binds medication remaining in the gastrointestinal tract and decreases serum concentrations by interrupting enteroenteric recirculation of theophylline. 1 Use of an aqueous activated charcoal preparation is recommended. If the total dose of OAC is not tolerated, more frequent administration of smaller doses, slow instillation through a nasogastric tube, or concurrent use of an antiemetic may be tried. 64

The initial dose of charcoal may be followed by a single dose of sorbitol if the charcoal is not pre-mixed with sorbitol. 65, 153 Caution is recommended when giving more than a single dose of sorbitol since frequent administration may result in dehydration and electrolyte imbalance secondary to diarrhea. Sorbitol is reported to be more effective than magnesium-containing cathartics and is not associated with hypermagnesemia; 65 however, the role of cathartics is questionable. 179

Ipecac syrup should generally be avoided in the management of theophylline overdoses. 152, 153

Gastric lavage is generally not necessary if the patient has vomited. Lavage may provide some benefit if performed via a large bore orogastric tube less than 1 hour after a large ingestion. This procedure may not be very effective for large, poorly soluble tablets. 64

Whole bowel irrigation with polyethylene glycol and electrolyte combination may be of some value if performed early in the treatment of large ingestions of extended-release dosage forms. Whole bowel irrigation with polyethylene glycol and electrolytes may also be useful when theophylline serum concentrations rapidly increase or when high concentrations persist despite other methods of removal. 64, 178

To enhance elimination¾ Repeated doses of OAC will at least double theophylline clearance 1 and should be continued throughout the course of toxicity, until the patient is asymptomatic and serum concentration is below 20 mcg/mL (110 micromoles/L). 64, 153

Extracorporeal elimination of theophylline by charcoal hemoperfusion is the most effective means of increasing theophylline clearance. Hemodialysis is less effective; however, it may be used if hemoperfusion is unavailable. 64 Peritoneal dialysis is considered ineffective. 1, 64, 153 Controversy exists about when to initiate extracorporeal elimination. 2, 53, 59 It may be indicated when serum theophylline concentrations are approaching 90 mcg/mL (495 micromoles/L) in an acute overdose 64 or when serum theophylline concentrations are greater than 40 mcg/mL (220 micromoles/L) in a chronic overdose or in certain patients with other significant risk factors, such as age greater than 60 years 66 or presence of complicating illness. In addition, use of extracorporeal elimination is recommended in the presence of intractable seizures or life-threatening cardiovascular symptoms, regardless of serum concentration. 64

Nausea or vomiting¾ The presence of nausea or vomiting should not cause postponement of OAC administration. Antiemetic therapy with metoclopramide or ondansetron, administered intravenously, may be useful. 64 See the package insert or the Metoclopramide (Systemic) or Ondansetron (Systemic) monograph for specific dosing guidelines for use of these products. Phenothiazine antiemetics such as

prochlorperazine or perphenazine should be avoided since they can lower the seizure threshold. 153, 181

Seizures¾ Seizures associated with serum concentrations > 30 mcg/mL (165 micromoles/L) are often resistant to anticonvulsant therapy and may produce a toxic encephalopathy and permanent brain damage if not rapidly controlled. An intravenous benzodiazepine is the drug of choice. See the package insert or the Benzodiazepines (Systemic) monograph for specific dosing guidelines for use of these products.

If seizures are repetitive or seizure prophylaxis is indicated in selected patients at high risk for theophylline-induced seizures, intravenous phenobarbital may be administered. In animal studies, the prophylactic use of phenobarbital in therapeutic doses has delayed the onset of theophylline-induced seizures and reduced mortality. There are no controlled studies in humans. See the package insert or the Barbiturates (Systemic) monograph for specific dosing guidelines for use of this product. Phenytoin is considered ineffective. 153

Should use of a benzodiazepine and phenobarbital fail to control seizure activity, the addition of the barbiturate anesthetic agent, thiopental, may be considered. Use of a neuromuscular blocking agent may also be considered to decrease the muscular manifestations of persistent seizures. General anesthesia should be used with caution because flourinated volatile anesthetics may sensitize the myocardium to endogenous catecholamines released by theophylline. Enflurane appears less likely to be associated with this effect than does halothane. 153 See the package insert or the Anesthetics, Inhalation (Systemic) , Anesthetics, Barbiturate (Systemic) , and/or Neuromuscular Blocking Agents (Systemic) monographs for specific dosing guidelines for use of these products. 64

Ventricular tachyarrhythmias¾ Ventricular tachyarrhythmias considered to be life-threatening require antiarrhythmic therapy specific for the type of arrhythmia. 64

Monitoring¾ Serial theophylline serum concentrations should be obtained to guide and assess treatment decisions. 64 Serial monitoring should continue at periodic intervals after treatment has been discontinued until it is clear that the serum concentration is no longer rising. Serious rebound theophylline toxicity has been reported, due to bezoar formation composed of undissolved extended-release tablets. 68

All monitoring interventions should be continued until the serum concentration remains below 20 mcg/mL (110 micromoles/L) 52, 64 and the patient is asymptomatic. 152

Abdominal physical examination should be performed to determine the presence of distention and/or the absence of bowel sounds when repeated doses of OAC are administered. 65 Arterial blood gases, electrocardiograph, serum electrolytes and glucose, stool output, and vital signs should also be monitored as required.

Supportive care¾ Respiration should be supported by airway management, oxygen administration, or mechanical ventilation as required, especially if higher doses of a benzodiazepine, phenobarbital, or a neuromuscular blocking agent are used.

Standard measures should be used to manage hypotension and metabolic complications.

Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Bronchodilators, Theophylline (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to theophylline bronchodilators or to ethylenediamine in aminophylline
Pregnancy¾Crosses placenta; decreased elimination during third trimester may require more frequent serum concentration determinations
Breast-feeding¾Distributes into breast milk; may result in irritability in infants
Use in children¾Decreased theophylline clearance in children less than 1 year of age, especially neonates and infants less than 3 months of age with renal function impairment, results in lower dosage requirements; initially, use in children less than 1 year of age may require more frequent serum concentration determinations
Use in the elderly¾Possible decreased theophylline clearance in patients 60 years of age or older may result in lower dosage requirements; severe signs or symptoms of toxicity are more common in these patients following chronic overdose that results in serum concentrations > 30 mcg per mL (165 micromoles per L)
Other medications, especially beta-adrenergic blocking agents; cimetidine; ciprofloxacin; clarithromycin; enoxacin; erythromycin; fluvoxamine; mexiletine; moricizine; pentoxifylline; phenytoin; rifampin; tacrine; thiabendazole; ticlopidine; or troleandomycin
Other medical problems, especially congestive heart failure, convulsions (seizures), hepatic disease, or hypothyroidism
Proper use of this medication

>> Proper administration
For liquids and immediate-release capsules or tablets: Taking on an empty stomach with a glass of water for faster absorption or, if necessary, taking with meals or immediately after meals to lessen gastrointestinal irritation, unless otherwise directed
For once-a-day dosage forms: Taking the medication either in the morning at least 1 hour before eating or in the evening with or without food, depending on the specific product; taking consistently with or without food; taking at approximately the same time each day
For enteric-coated or delayed-release tablet dosage form: Swallowing tablets whole; not breaking (unless scored for breakage), crushing, or chewing
For extended-release dosage forms: Swallowing capsules whole or opening capsules and sprinkling contents on soft food, then swallowing without crushing or chewing; not breaking (unless scored for breakage), crushing, or chewing tablets; taking on an empty stomach with a glass of water for faster absorption or, if necessary, taking with meals or immediately after meals to lessen gastrointestinal irritation, unless otherwise directed

>> Importance of not using more than amount prescribed

>> Compliance with therapy; not missing doses

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician required to check progress, including blood levels

>> Not changing brands or dosage forms without first checking with physician

>> Notifying physician of factors that may alter theophylline concentrations, such as:
¾fever (³102 °F ³ 24 hours or a lower temperature elevation for a longer period)
¾other medicines started or stopped
¾smoking started or stopped
¾an extended change in diet

Caution in eating or drinking large amounts of caffeine-containing foods or beverages during therapy with this medication

Side/adverse effects

Signs of potential side effects, especially heartburn and/or vomiting, hives, skin rash, and sloughing of skin

Signs of toxicity

General Dosing Information

The bronchodilator action of aminophylline, oxtriphylline, and theophylline depends upon their theophylline content. The anhydrous theophylline content of various theophylline salts is as follows:
Aminophylline anhydrous¾86%. 78

Aminophylline dihydrate¾79%. 78

Oxtriphylline¾64%. 78

Theophylline monohydrate¾91%.
Theophylline does not distribute into fatty tissue; therefore, all dosages should be calculated on the basis of lean (ideal) body weight. 1, 49, 77

The recommended doses are given as a guideline for use in the average patient. Dosage of aminophylline, oxtriphylline, or theophylline must be adjusted to meet the individual requirements of each patient on the basis of product selected, patient characteristics, clinical response, and steady-state serum theophylline concentrations.
Administration of a single loading dose of theophylline is intended to produce a serum concentration in the therapeutic range as quickly as possible. A theophylline loading dose may be considered for all patient groups 49 , including neonates 63.

Although the intravenous route of administration provides the most rapid effect, immediate-release oral liquids, tablets, or capsules may also be used. 1, 5, 62 Delayed- or extended-release dosage forms should not be used when rapid achievement of a therapeutic serum theophylline concentration is required. 72

Before a loading dose is administered, it is extremely important to determine the time, amount, dosage form, and route of administration of previous doses of aminophylline, oxytriphylline, or theophylline. Once the desired theophylline serum concentration is obtained with a loading dose, it can be maintained with an oral or intravenous dosage form. 8

The goal of chronic therapy is to obtain maximum potential benefit with minimal risk of adverse effects. Transient caffeine-like side effects and excessively high serum concentrations can be avoided in most patients by starting with a lower dose and slowly increasing the dose by 25% at three-day intervals, approximately.
For final dosage adjustment in chronic therapy after serum theophylline measurement, the following dosage adjustments are recommended: 153

Steady-state Peak Serum Theophylline Concentration (mcg/mL)	Recommended Dosage Adjustment
Below 9.9	If clinically indicated, about 25% increase to nearest dose increment; recheck serum theophylline concentration after 3 days for further dosage adjustment
10-14.9	If clinically indicated, maintain dose and recheck serum theophylline concentration at 6- to 12-month intervals; if symptoms are not controlled, consider adding additional medication to treatment regimen
15-19.9	Consider 10% decrease in dose to increase margin of safety even if current dosage is tolerated
20-24.9	Decrease dose by 25% even if no adverse effects are present; recheck serum theophylline concentration after 3 days
25-30	Omit next dose; 25% decrease in subsequent doses even if no adverse effects are present; recheck serum theophylline concentration after 3 days; if symptomatic, consider whether overdose treatment is indicated
> 30	Treatment of overdose may be indicated; when theophylline is resumed, decrease subsequent dose by at least 50%; recheck serum theophylline concentration after 3 days

Note: If asthma is well controlled and there are no side effects or intervening factors that would alter dose requirements, follow-up serum concentration measurements can be obtained at 6- to 12-month intervals. However, whenever a patient develops nausea, vomiting, CNS stimulation or any other symptom of theophylline toxicity, even if another cause is suspected (e.g., viral gastroenteritis), the next dose should be withheld and a serum concentration measurement obtained. In addition, various drug interactions and physiologic abnormalities can alter theophylline elimination and require serum concentration measurement and/or dose adjustment. 54, 71, 77

For oral dosage forms only

The dosing frequency should be individualized. When rapidly absorbed dosage forms such as liquids or immediate-release capsules or tablets are used, dosing to maintain therapeutic serum concentrations usually requires administration every 6 hours, especially in children and smoking adults. A dosing interval of up to 8 hours may be appropriate in some nonsmoking adults, elderly or debilitated patients, and neonates due to a slower clearance rate. In premature neonates and patients with hepatic disease, dosing every 12 hours or longer will usually provide relatively constant serum concentrations.
Patients requiring higher-than-usual doses (i.e., patients with rapid clearance rates) may be more effectively controlled during chronic therapy by being given extended-release dosage forms. These products have the potential to achieve relatively constant serum concentrations with 12-hour dosing intervals. Patients who metabolize theophylline rapidly may require an extended-release product every 8 hours. Patients who metabolize theophylline at a normal or slow rate (elimination half-life longer than 8 hours) 162 are potential candidates for once-a-day formulations. 6

Alcohol-free liquid dosage forms are generally preferred.
For patients who have difficulty in swallowing, some extended-release capsules may be opened and the contents sprinkled on a spoonful of soft, cold food such as applesauce or pudding, then taken without chewing. 6, 73, 74

For parenteral dosage forms only

Therapy can be converted from an intravenous to an oral product by dividing the total daily dose that produced the desired steady-state peak serum concentration into equal parts, and giving in amounts and at intervals appropriate for the product. The intravenous infusion can usually be discontinued when the first oral dose of medication is administered. 1, 67, 123 Extreme caution is recommended if intravenous and oral therapy are overlapped, since this practice may lead to inadvertent theophylline toxicity. 164, 180

Use of intravenous aminophylline or theophylline should be reassessed after 24 to 72 hours. Oral therapy should be substituted for intravenous therapy as soon as the patient is able to take medication orally. 175

Diet/Nutrition

Dietary changes are of clinical importance only if a sustained and extreme change in the usual eating pattern occurs. 5 High-carbohydrate, low-protein diets have been shown to decrease theophylline

elimination. Low-carbohydrate, high-protein diets and daily ingestion of charcoal-broiled beef have been shown to increase theophylline elimination. 54

Large amounts of caffeine-containing foods or beverages should be avoided, since they may increase CNS stimulant effects of theophylline bronchodilators. 8

Bioequivalence information

For oral dosage forms only¾ The formulation selected for maintenance therapy can have an important effect on the serum concentration-time profile. Selection of a theophylline product must be based upon the specific clinical indication, the absorption characteristics of the formulation, and the rate of theophylline elimination in the individual patient. Immediate-release oral formulations can generally be used interchangeably since they are not considered to have clinically important differences in rates of absorption. 5 However, many brands of extended-release theophylline products have clinically important differences in their extent and/or rate of absorption. Different extended-release products having the same strength of active ingredient may not be equivalent due to formulation differences. Even with reliably absorbed extended-release formulations, a minority of patients can have marked day-to-day variations in absorption. When this occurs, alternative therapy should be considered.

Due to the significant variability in extended-release product characteristics, pharmacists should not substitute one brand for another without consulting the prescribing physician unless the product has proven bioequivalence, so that theophylline serum concentrations can be appropriately monitored. 54

AMINOPHYLLINE

Summary of Differences

Category¾ Aminophylline (injection, oral solution) is also used as a respiratory stimulant in neonatal apnea; aminophylline injection is used as an antidote to dipyridamole toxicity.

Pharmacology/pharmacokinetics¾ Aminophylline is a theophylline compound with ethylenediamine.

Aminophylline releases free theophylline at physiologic pH.

Side/adverse effects¾ Ethylenediamine in aminophylline may cause hives, skin rash, or sloughing of skin.

General dosing information¾ Aminophylline anhydrous contains about 86% of anhydrous theophylline.

Aminophylline dihydrate contains about 79% of anhydrous theophylline.

Additional Dosing Information

See also General Dosing Information.

The recommended doses are given as a guideline for use in the average patient. Dosage of aminophylline must be adjusted to meet the individual requirements of each patient on the basis of product selected, patient characteristics, clinical response, and steady-state serum theophylline concentrations.

For parenteral dosage forms only

Intramuscular administration of aminophylline injection is not recommended since precipitation may occur at the site of injection, resulting in severe local pain and slow absorption. 5

Aminophylline may be administered by direct intravenous injection or by intravenous infusion; however, it is recommended that intravenous aminophylline be administered slowly, at a rate not exceeding 25 mg per minute. 101

For rectal dosage forms only

USP DI Advisory Panels do not recommend the use of aminophylline suppositories because of the potential for slow and unreliable absorption. The suppositories may also cause local irritation.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

AMINOPHYLLINE ORAL SOLUTION USP

Usual adult dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. After three days, the dosage may be increased, if tolerated, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. 153

The total daily adult dose is administered in three or four divided doses given about six to eight hours apart. Patients with risk factors for impaired theophylline clearance may require a dosing interval of every twelve hours. Young adult smokers and patients with more rapid metabolism may require a dosing interval of every six hours.

Note:

If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean

(ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours. 153

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours. 153

Full-term infants, postnatal age up to 52 weeks 153 ¾Oral, the equivalent of anhydrous theophylline: total daily dose in mg per kg of body weight = (0.2)(postnatal age in weeks) + 5.
Note:
For full-term infants up to 26 weeks of age, divide the total daily dose into three equal amounts administered eight hours apart.
For full-term infants 26 to 52 weeks of age, divide the total daily dose into four equal amounts administered six hours apart.
Children 1 year of age and older, weighing less than 45 kg 153 ¾Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight, up to a maximum of 600 mg, per day. The total daily dose is administered in four to six divided doses and given every four to six hours.
Children weighing more than 45 kg¾See Usual adult dose.
153

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
[Respiratory stimulant (neonatal apnea)] *¾Loading dose¾ For patients not currently receiving theophylline preparations¾Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 1, 153, 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours 153.

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours 153.

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾105 mg of anhydrous aminophylline (equivalent to 90 mg of anhydrous theophylline) per 5 mL (Rx) [Generic]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

AMINOPHYLLINE TABLETS USP

Usual adult dose

See Aminophylline Oral Solution USP.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours. 153

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours. 153

Full-term infants, postnatal age up to 52 weeks 153 ¾Oral, the equivalent of anhydrous theophylline: total daily dose in mg per kg of body weight = (0.2)(postnatal age in weeks) + 5.
Note:

For full-term infants up to 26 weeks of age, divide the total daily dose into three equal amounts administered eight hours apart.

For full-term infants 26 to 52 weeks of age, divide the total daily dose into four equal amounts administered six hours apart.

Children 1 year of age and older, weighing less than 45 kg 153 ¾Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight, up to a maximum of 600 mg, per day. The total daily dose is administered in four to six divided doses and given every four to six hours.

Children weighing more than 45 kg¾See Usual adult dose.
153

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾100 mg of hydrous aminophylline (equivalent to 79 mg of anhydrous theophylline) (Rx) [Generic] (may be scored)

200 mg of hydrous aminophylline (equivalent to 158 mg of anhydrous theophylline) (Rx) [Generic] (may be scored)

Canada¾100 mg of hydrous aminophylline (equivalent to 79 mg of anhydrous theophylline) (Rx) [Generic] (may be scored)

200 mg of hydrous aminophylline (equivalent to 158 mg of anhydrous theophylline) (Rx) [Generic] (may be scored)

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

AMINOPHYLLINE EXTENDED-RELEASE TABLETS

Usual adult dose

Bronchodilator¾Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. One-half of the daily dose may be given at twelve-hour intervals. However, certain patients metabolize theophylline more rapidly, especially the young and those who smoke, and may require dosing at eight-hour intervals. 153

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Bronchodilator¾Children up to 6 years of age: Use is not recommended. 145

Children 6 to 16 years of age: See Usual adult dose .

Strength(s) usually available

U.S.¾225 mg of hydrous aminophylline (equivalent to 178 mg of anhydrous theophylline) (Rx)[Phyllocontin (scored)]

Canada¾225 mg of hydrous aminophylline (equivalent to 182.25 mg of anhydrous theophylline) (Rx)[Phyllocontin (scored)]

350 mg of hydrous aminophylline (equivalent to 283.5 mg of anhydrous theophylline (Rx)[Phyllocontin-350 (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

AMINOPHYLLINE INJECTION USP

Usual adult dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose, infused over twenty to thirty minutes, 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per ml (27.5 to 82.5 micromoles per L). 1, 49, 153

  For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Young adult smokers¾Intravenous infusion, the equivalent of anhydrous theophylline, 700 mcg (0.7 mg) per kg of body weight per hour 80, 146.

Otherwise healthy nonsmoking adults¾Intravenous infusion, the equivalent of anhydrous theophylline, 400 mcg (0.4 mg) per kg of body weight per hour 80, 146.

Older patients and patients with cardiac decompensation, cor pulmonale, or hepatic function impairment¾Intravenous infusion, the equivalent of anhydrous theophylline, 200 mcg (0.2 mg) per kg of body weight per hour 80, 146.

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
Antidote (to dipyridamole toxicity) *¾Intravenous, the equivalent of 50 to 100 mg (range, 50 mg up to a maximum dose of 250 mg) administered over thirty to sixty seconds. 123

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Children up to 16 years of age: Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose over twenty to thirty minutes 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Intravenous, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours 80, 146.

Premature infants, postnatal age 24 days and older¾Intravenous, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours 80, 146.

Full-term infants, postnatal age up to 52 weeks 153 ¾Intravenous, the equivalent of anhydrous theophylline, total daily dose in mg per kg of body weight = (0.2)(postnatal age in weeks) + 5.
For full-term infants up to 26 weeks of age, divide the total daily dose into three equal amounts administered eight hours apart. For full-term infants 26 to 52 weeks of age, divide the total daily dose into four equal amounts administered six hours apart.
Note:
May also be administered to infants less than 1 year as an intravenous infusion, the equivalent of anhydrous theophylline, dose in mg per kg of body weight per hour = (0.008)(age in weeks) + 0.21. 174

Children 1 to 9 years of age¾Intravenous infusion, the equivalent of anhydrous theophylline, 800 mcg (0.8 mg) per kg of body weight per hour 80, 146.

Children 9 to 16 years¾Intravenous infusion, the equivalent of anhydrous theophylline, 700 mcg (0.7 mg) per kg of body weight per hour 80, 146.

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
 [Respiratory stimulant (neonatal apnea)] *¾Loading dose¾ For patients not currently receiving theophylline preparations¾Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose over twenty to thirty minutes 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

  For patients currently receiving theophylline preparations: Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Intravenous, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours 80, 146.

  Premature infants, postnatal age 24 days and older¾Intravenous, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours 80, 146.

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾25 mg of hydrous aminophylline (equivalent to 19.7 mg of anhydrous theophylline) per mL (Rx) [Generic]

Canada¾25 mg of hydrous aminophylline (equivalent to 19.7 mg of anhydrous theophylline) per mL (Rx) [Generic]

50 mg of hydrous aminophylline (equivalent to 39.4 mg of anhydrous theophylline) per mL (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

To dilute the injection for intravenous administration, dextrose 5% in water, sodium chloride, or dextrose-sodium chloride combinations may be used. 101

Stability:

A slight yellowing of the solution can occur when aminophylline is added to some dextrose-containing solutions. Because the aminophylline content remains constant, the discoloration is believed to result from the decomposition of dextrose. 101

Aminophylline solutions whose concentration does not exceed 40 mg/mL are reported to be stable for at least 48 hours at 77 °F (25 °C). 101

Incompatibilities:

Although aminophylline has been reported to precipitate in acidic media, this generally does not apply to the dilute solutions for intravenous infusions. 101

No additives should be made directly to the same intravenous bag or bottle of aminophylline because dosages are titrated to response, and because admixture incompatibilities exist with a number of other medications.
Doxapram hydrochloride is reported to be incompatible with aminophylline when combined in the same syringe. 101

Medications that are incompatible when injected into Y-sites of administration sets with a continuous infusion of aminophylline include amiodarone hydrochloride, ciprofloxacin, diltiazem hydrochloride, dobutamine hydrochloride, hydralazine hydrochloride, and ondansetron hydrochloride. 101

Rectal Dosage Forms

AMINOPHYLLINE SUPPOSITORIES USP

Note: USP DI Advisory Panels do not recommend the use of Aminophylline Suppositories USP because of the potential for slow and unreliable absorption.
Strength(s) usually available

U.S.¾250 mg of hydrous aminophylline (equivalent to 197.5 mg of anhydrous theophylline) (Rx)[Truphylline] [Generic]

500 mg of hydrous aminophylline (equivalent to 395 mg of anhydrous theophylline) (Rx)[Truphylline] [Generic]

Canada¾Not commercially available.

OXTRIPHYLLINE

Summary of Differences

Pharmacology/pharmacokinetics¾ Oxtriphylline is the choline salt of theophylline.
Oxtriphylline releases free theophylline at physiologic pH.

General dosing information¾ Oxtriphylline contains about 64% of anhydrous theophylline.

Additional Dosing Information

See also General Dosing Information.

The recommended doses are given as a guideline for use in the average patient. Dosage of oxtriphylline must be adjusted to meet the individual requirements of each patient on the basis of product selected, patient characteristics, clinical response, and steady-state serum theophylline concentrations.

Oral Dosage Forms

OXTRIPHYLLINE ORAL SOLUTION USP

Usual adult dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

  For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. After three days, the dosage may be increased, if tolerated, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. 153

  The total daily adult dose is administered in three or four divided doses given about six to eight hours apart. Patients with risk factors for impaired theophylline clearance may require a dosing interval of every twelve hours. Young adult smokers and patients with more rapid metabolism may require a dosing interval of every six hours. 54

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic oxtriphylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Use is not recommended in children due to high alcohol content.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾100 mg (equivalent to 64 mg of anhydrous theophylline) per 5 mL (Rx)[Choledyl (alcohol 20%)] [PMS-Oxtriphylline (alcohol 20%)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from freezing.

OXTRIPHYLLINE SYRUP

Usual adult dose

See Oxtriphylline Oral Solution USP.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg/mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours 153.

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours 153.

Full-term infants, postnatal age up to 52 weeks¾Oral, the equivalent of anhydrous theophylline: Total daily dose in mg per kg of body weight = (0.2)(postnatal age in weeks) + 5. 153

Note:
For full-term infants up to 26 weeks of age, divide the total daily dose into three dosing intervals, eight hours apart.
For full-term infants 26 to 52 weeks of age, divide the total daily dose into four dosing intervals six hours apart.
Children 1 year of age and older, but weighing less than 45 kg¾Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600 mg per day. The total daily dose is administered in four to six divided doses given every four to six hours. 153

Children weighing more than 45 kg¾See Usual adult dose .

Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic oxtriphylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾Not commercially available.
Canada¾50 mg (equivalent to 32 mg of anhydrous theophylline) per 5 mL (Rx)[Choledyl] [PMS-Oxtriphylline]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from freezing.

OXTRIPHYLLINE TABLETS

Usual adult dose

See Oxtriphylline Oral Solution USP.

Usual pediatric dose

See Oxtriphylline Syrup.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾100 mg (equivalent to 64 mg of anhydrous theophylline) (Rx)[Apo-Oxtriphylline]

200 mg (equivalent to 128 mg of anhydrous theophylline) (Rx)[Apo-Oxtriphylline] [Choledyl]

300 mg (equivalent to 192 mg of anhydrous theophylline) (Rx)[Apo-Oxtriphylline]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

OXTRIPHYLLINE DELAYED-RELEASE TABLETS USP

Usual adult dose

Bronchodilator¾Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. The total daily adult dose is administered in three or four divided doses given about six to eight hours apart. Patients with risk factors for impaired theophylline clearance may require a dosing interval of every

twelve hours. Young adult smokers and patients with more rapid metabolism may require a dosing interval of every six hours. 153

Usual pediatric dose

Bronchodilator¾Children up to 6 years of age: Use is not recommended in children up to 6 years of age since this age group may not be capable of swallowing the tablets whole.
Children 6 to 16 years of age: See Usual adult dose .

Strength(s) usually available

U.S.¾100 mg (equivalent to 64 mg of anhydrous theophylline) (Rx)[Choledyl (enteric, sugar-coated)]

200 mg (equivalent to 127 mg of anhydrous theophylline) (Rx)[Choledyl (enteric, sugar-coated)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Swallow tablets whole.

OXTRIPHYLLINE EXTENDED-RELEASE TABLETS USP

Usual adult dose

Bronchodilator¾Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. One-half of the daily dose may be given at twelve-hour intervals. However, certain patients metabolize theophylline more rapidly, especially the young and those that smoke, and may require dosing at eight-hour intervals. 153

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic oxtriphylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Bronchodilator¾Children up to 6 years of age: Use is not recommended. 76

Children 6 to 16 years of age: See Usual adult dose .

Strength(s) usually available

U.S.¾400 mg (equivalent to 254 mg of anhydrous theophylline) (Rx)[Choledyl SA (confectioner"s sugar)]

600 mg (equivalent to 382 mg of anhydrous theophylline) (Rx)[Choledyl SA (confectioner"s sugar)]

Canada¾400 mg (equivalent to 254 mg of anhydrous theophylline) (Rx)[Choledyl SA (scored)]

600 mg (equivalent to 382 mg of anhydrous theophylline) (Rx)[Choledyl SA (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

THEOPHYLLINE

Summary of Differences

Category: Theophylline oral liquids are also used as a respiratory stimulant in neonatal apnea.

Additional Dosing Information

See also General Dosing Information.

The recommended doses are given as a guideline for use in the average patient. Dosage of theophylline must be adjusted to meet the individual requirements of each patient on the basis of product selected, patient characteristics, clinical response, and steady-state serum theophylline concentrations.
For parenteral dosage forms only

The rate of administration of theophylline and dextrose injection should not exceed 25 mg per minute.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

THEOPHYLLINE CAPSULES USP

Usual adult dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L. 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of

theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. After three days, the dosage may be increased, if tolerated, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. 153

The total daily adult dose is administered in three or four divided doses given about six to eight hours apart. Patients with risk factors for impaired theophylline clearance may require a dosing interval of every twelve hours. Young adult smokers and patients with more rapid metabolism may require a dosing interval of every six hours. 54

Note:
If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Children 1 year of age and older, weighing less than 45 kg¾Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600 mg, per day. The total daily dose is administered in four to six divided doses given every four to six hours. 153

Children weighing more than 45 kg¾See Usual adult dose 153.

Note:
If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Strength(s) usually available

U.S.¾100 mg (equivalent of anhydrous theophylline) (Rx)[Elixophyllin] [Generic]

200 mg (equivalent of anhydrous theophylline) (Rx)[Elixophyllin] [Generic]

300 mg (equivalent of anhydrous theophylline) (Rx) [Generic]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

THEOPHYLLINE EXTENDED-RELEASE CAPSULES USP

Note: Due to the significant variability in extended-release product characteristics, pharmacists should not substitute one brand for another without consulting the prescribing physician unless the product has proven bioequivalence, so that theophylline serum concentrations can be appropriately monitored. 54

Usual adult dose

Bronchodilator¾Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. One-half of the daily theophylline dose may be given at twelve-hour intervals. However, certain patients metabolize theophylline more rapidly, especially the young and those that smoke, and may require dosing at eight-hour intervals. 54, 74, 153

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Bronchodilator¾Children 1 year of age and older, weighing less than 45 kg: Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600 mg, per day. One-half of the daily theophylline dose may be given as aminophylline at twelve-hour intervals. However, younger patients may require dosing at eight-hour intervals. 153

Children weighing more than 45 kg: See Usual adult dose.
153

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾50 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

75 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

100 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps] [Theo-24]

125 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps] [Theovent Long-Acting]

200 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps] [Theo-24]

250 mg (equivalent of anhydrous theophylline) (Rx)[Theovent Long-Acting]

260 mg (equivalent of anhydrous theophylline) (Rx)[Aerolate Sr] [Theobid Duracaps]

300 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps] [Theo-24]

400 mg (equivalent of anhydrous theophylline) (Rx)[Theo-24]

Canada¾50 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

100 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

200 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

300 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Bid Gyrocaps]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Additional information:

Certain extended-release capsules may be opened and the contents sprinkled on soft food immediately prior to ingestion, then swallowed without crushing or chewing. Capsule contents should not be subdivided.

THEOPHYLLINE ELIXIR

Usual adult dose

See Theophylline Capsules USP.

Usual pediatric dose

Use is not recommended in children due to the high alcohol content.

Strength(s) usually available

U.S.¾27 mg (equivalent of anhydrous theophylline) per 5 mL (Rx)[Asmalix (alcohol 20%)] [Elixophyllin (alcohol 20%)] [Lanophyllin (alcohol 20%)] [Truxophyllin] [Generic]

Canada¾27 mg (equivalent of anhydrous theophylline) per 5 mL (Rx)[PMS Theophylline (alcohol 18%)] [Pulmophylline (alcohol 20% [v/v])] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Exposure to cold temperatures may cause theophylline crystallization to occur. At room temperature the crystals redissolve and solution gradually clears.

Auxiliary labeling:

· Do not refrigerate.

THEOPHYLLINE ORAL SOLUTION

Usual adult dose

See Theophylline Capsules USP.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours. 80

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours. 80

Full-term infants, postnatal age up to 52 weeks¾Oral, the equivalent of anhydrous theophylline: total daily dose in mg per kg of body weight = (0.2)(postnatal age in weeks) + 5. 80

Note:
For full-term infants up to 26 weeks of age, divide the total daily dose into three equal amounts administered eight hours apart.
For full-term infants 26 to 52 weeks of age, divide the total daily dose into four equal amounts administered six hours apart.
Children 1 year of age and older, weighing less than 45 kg: Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600 mg, per day. The total daily dose is administered in four to six divided doses given every four to six hours. 153

Children weighing more than 45 kg: See Usual adult dose.
153

Note:
If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
[Respiratory stimulant (neonatal apnea)] *¾Loading dose¾ For patients not currently receiving theophylline preparations¾Infants and children up to 16 years of age: Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Premature infants, postnatal age less than 24 days¾Oral, the equivalent of 1 mg of anhydrous theophylline per kg of body weight every twelve hours. 80, 146

Premature infants, postnatal age 24 days and older¾Oral, the equivalent of 1.5 mg of anhydrous theophylline per kg of body weight every twelve hours. 80, 146

Note:
If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
Strength(s) usually available

U.S.¾27 mg (equivalent of anhydrous theophylline) per 5 mL (Rx)[Theolair] [Generic]

Canada¾27 mg (equivalent of anhydrous theophylline) per 5 mL (Rx)[Theolair]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Exposure to cold temperatures may cause theophylline crystallization to occur. At room temperature the crystals redissolve and solution gradually clears.

Auxiliary labeling:

· Do not refrigerate.

THEOPHYLLINE SYRUP

Usual adult dose

See Theophylline Capsules USP.

Usual pediatric dose

See Theophylline Oral Solution .

Strength(s) usually available

U.S.¾27 mg (equivalent of anhydrous theophylline) per 5 mL (Rx)[Slo-Phyllin]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Exposure to cold temperatures may cause theophylline crystallization to occur. At room temperature the crystals redissolve and solution gradually clears.

Auxiliary labeling:

· Do not refrigerate.

THEOPHYLLINE TABLETS USP

Usual adult dose

See Theophylline Capsules USP.

Usual pediatric dose

See Theophylline Capsules USP.

Strength(s) usually available

U.S.¾100 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Phyllin (scored)] [Generic]

125 mg (equivalent of anhydrous theophylline) (Rx)[Theolair (scored)]

200 mg (equivalent of anhydrous theophylline) (Rx)[Slo-Phyllin (scored)] [Generic]

250 mg (equivalent of anhydrous theophylline) (Rx)[Theolair (scored)]

300 mg (equivalent of anhydrous theophylline) (Rx)[Quibron-T Dividose (scored)] [Generic]

Canada¾125 mg (equivalent of anhydrous theophylline) (Rx)[Theolair (scored)]

250 mg (equivalent of anhydrous theophylline) (Rx)[Theolair (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

THEOPHYLLINE EXTENDED-RELEASE TABLETS

Note: Due to the significant variability in extended-release product characteristics, pharmacists should not substitute one brand for another without consulting the prescribing physician unless the product has proven bioequivalence, so that theophylline serum concentrations can be appropriately monitored. 54

Usual adult dose

Bronchodilator¾Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. One-half the daily theophylline dose may be given at twelve hour intervals. However, certain patients metabolize theophylline more rapidly, especially the young and those that smoke, and may require dosing at eight hour intervals.

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Bronchodilator¾Children 1 year of age and older, weighing less than 45 kg: Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600 mg, per day. One-half of the daily theophylline dose may be given at twelve-hour intervals. However, younger patients may require dosing at eight-hour intervals. 153

Children weighing more than 45 kg: See Usual adult dose.
153

Children 6 to 16 years of age: See Usual adult dose .
153

Strength(s) usually available

U.S.¾100 mg (equivalent of anhydrous theophylline) (Rx)[Theochron (scored)] [Theo-Dur (scored)] [Theo-Time] [Theo-X] [Generic]

200 mg (equivalent of anhydrous theophylline) (Rx)[Theochron (scored)] [Theo-Dur (scored)] [Theolair-SR (scored)] [Theo-Time] [Theo-X] [T-Phyl (scored)] [Generic]

250 mg (equivalent of anhydrous theophylline) (Rx)[Respbid (scored)] [Theolair-SR (scored)]

300 mg (equivalent of anhydrous theophylline) (Rx)[Quibron-T/SR Dividose (scored)] [Theochron (scored)] [Theo-Dur (scored)] [Theolair-SR (scored)] [Theo-Time] [Theo-X] [Generic]

400 mg (equivalent of anhydrous theophylline) (Rx)[Uni-Dur (scored)] [Uniphyl (scored)]

450 mg (equivalent of anhydrous theophylline) (Rx)[Theo-Dur (scored)] [Generic] (may be scored)

500 mg (equivalent of anhydrous theophylline) (Rx)[Respbid (scored)] [Theolair-SR (scored)]

600 mg (equivalent of anhydrous theophylline) (Rx)[Uni-Dur (scored)]

Canada¾100 mg (equivalent of anhydrous theophylline) (Rx)[Apo-Theo LA (scored)] [Theochron (scored)] [Theo-Dur (scored)]

200 mg (equivalent of anhydrous theophylline) (Rx)[Apo-Theo LA (scored)] [Theochron (scored)] [Theo-Dur (scored)] [Theolair-SR (scored)] [Theo-SR (scored)]

250 mg (equivalent of anhydrous theophylline) (Rx)[Theolair SR (scored)]

300 mg (equivalent of anhydrous theophylline) (Rx)[Apo-Theo LA (scored)] [Quibron-T/SR Dividose (scored)] [Theochron (scored)] [Theo-Dur (scored)] [Theolair-SR (scored)] [Theo-SR (scored)]

400 mg (equivalent of anhydrous theophylline) (Rx)[Uniphyl (scored)]

450 mg (equivalent of anhydrous theophylline) (Rx)[Theo-Dur (scored)]

500 mg (equivalent of anhydrous theophylline) (Rx)[Theolair-SR (scored)]

600 mg (equivalent of anhydrous theophylline) (Rx)[Uniphyl (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Swallow tablets whole, unless otherwise directed.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

THEOPHYLLINE IN DEXTROSE INJECTION USP

Usual adult dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose, infused over 20 to 30 minutes, 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (range 27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Young adult smokers¾Intravenous infusion, the equivalent of anhydrous theophylline: 700 mcg (0.7 mg) per kg of body weight per hour 80, 146

Otherwise healthy nonsmoking adults¾Intravenous infusion, the equivalent of anhydrous theophylline: 400 mcg (0.4 mg) per kg of body weight per hour. 80, 146

Older patients and patients with cardiac decompensation, cor pulmonale, or hepatic function impairment¾Intravenous infusion, the equivalent of anhydrous theophylline: 200 mcg (0.2 mg) per kg of body weight per hour. 80, 146

Note:

If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Usual pediatric dose

Bronchodilator¾Loading dose¾ For patients not currently receiving theophylline preparations¾ Children 1 to 16 years of age: Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight 1, 78, 81 as a single dose over twenty to thirty minutes 49, 62 to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L). 1, 49, 153

For patients currently receiving theophylline preparations¾Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. 154 Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration. 1, 49

Maintenance¾ Full-term infants, postnatal age up to 52 weeks¾Intravenous infusion, the equivalent of anhydrous theophylline: Dose in mg per kg of body weight per hour = (0.008)(age in weeks) + 0.21. 174

Children 1 to 9 years of age¾Intravenous infusion, the equivalent of anhydrous theophylline: 800 mcg (0.8 mg) per kg of body weight per hour 80, 146.

Children 9 to 16 years¾Intravenous infusion, the equivalent of anhydrous theophylline: 700 mcg (0.7 mg) per kg of body weight per hour 80, 146.

Note:

If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Strength(s) usually available

U.S.¾Theophylline in 5% dextrose injection (Rx) [GENERIC] contains the following amounts of anhydrous theophylline:

Volume (approx.) mL	Theophylline Anhydrous	
	Total mg	mg/mL
50	200	4
100	200	2
100	400	4
250	400	1.6
250	800	3.2
500	400	0.8
500	800	1.6

1000	400	0.4
1000	800	0.8

Canada-

Theophylline in 5% dextrose injection (Rx) [GENERIC] contains the following amounts of anhydrous theophylline:

Volume (approx.) mL	Theophylline Anhydrous	
	Total mg	mg/mL
50	200	4
100	200	2
100	400	4
250	400	1.6
500	400	0.8
500	800	1.6
1000	400	0.4
1000	800	0.8

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Theophylline and dextrose solutions contain no bacteriostatic, antimicrobial agent, or added buffer; they are intended only for single-dose administration. When smaller doses are required, the unused portion should be discarded.

Incompatibilities:

No additives should be made to theophylline and dextrose injection because dosages are titrated to response.
Hetastarch has been shown to be incompatible with theophylline in dextrose solution when injected into Y-sites of administration sets. 101

* Not included in Canadian product labeling.

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