

Aminophylline Injection USP

(Aminophylline Injection, USP)

25 and 50 mg/mL

Bronchodilator

Pharmacology: Theophylline is an alkaloid of the methylxanthine group. Aminophylline complexe of theophylline with ethylenediamine. Aminophylline dissociates in biological fluids to yield theophylline.

Theophylline’s principle pharmacologic actions include; stimulation of the CNS, stimulation of cardiac muscle relaxation of bronchial smooth muscle and diuresis. The mechanism of action is still unknown, however the three basic cellular effects of theophylline are; translocation of intracellular calcium, accumulation of cyclic AMP and adenosine receptor blockade. The accumulation of cyclic AMP increases the release of endogenous epinephrine resulting in increased beta-adrenergic stimulation. The methylxanthines have also been reported to potentiate inhibition of the synthesis of contractile prostaglandins.

Pharmacokinetics: The absorpton of theophylline administered I.M. is usually slow and incomplete. I.M. theophylline is extremely painful and is not recommended.

Theophylline is distributed throughout extracellular fluids and body tissues, it does not distribute into fatty tissue. Theophylline readily crosses the placenta and is secreted into breast milk in concentrations approaching 70% those in maternal serum. The average volume of distribution (Vd) is reported to be 0.45 L/kg for children and adults. At therapeutic concentrations plasma protein binding is approximately 60%, in neonates and patients with hepatic cirrhosis protein binding is reduced to approximately 35%.

Theophylline undergoes hepatic biotransformation via the cytochrom P-450 component of the microsomal oxidative enzyme system, to 1,3-dimethyluric acid, 1-methyluric acid and 3-methylxanthine, which are then excreted by the kidney. Metabolites account for approximately 85%, renal elimination of unchanged drug being less than 15%.

Theophylline clearance is markedly reduced in neonates. Neonates excrete a larger proportion of unchanged theophylline in the urine and dosage must be adjusted for renal failure in neonates. Theophylline half-life is much longer in neonates which allow for dosing intervals of every 12 hours. Theophylline clearance increases during the first year of life and remains relatively constant during the first 9 years of life thereafter, decreasing to adult values by age 16. Clearance is decreased in hepatic cirrhosis, acute hepatitis, cholestasis, heart failure, cor pulmonate, febrile respiratory tract infections and geriatrics. Cigarette or marijuana smokers have a more rapid clearance. Patients ingesting diets low in carbohydrates and high in protein or charcoal broiled meats also have an increased ability to clear theophylline.

Table I		
Average plasma half-life of theophylline		
Adults (healthy, nonsmoking)	7-9 hours	
Adults (smokers)	4-5 hours	
Children	3-5 hours	
Neonates (premature)	20-30 hours	

Variability between patients is great. Steady state is usually achieved by 48 hours with a consistent dosage schedule. In patients receiving treatment for acute conditions, in neonates or patients at risk of low theophylline clearance, serum, concentrations may be followed more closely regardless of steady state. The therapeutic plasma concentration range is between 55 to 110 µmol/L in children and adults. The upper end for neonates is generally closer to 55 mmol/L but must be individualized depending on the condition treated and the individual tolerance. Generally the peak concentration should be monitored for clinical guidance. The peak level yields information about potential for toxicity and efficacy of the dosage regimen. If the patient becomes symptomatic at the end of the dosing interval a trough concentration may be taken to determine whether or not the patients dosing interval is appropriate.

Saliva concentrations are not a reliable indicator of serum concentrations.

Concurrent administration of other drugs and xanthine containing beverages can affect some assay results measured by spectrophotometric methods. These substances do not interfere with results when measured by high-pressure liquid chromatography or EMIT.

Indications: The symptomatic treatment of reversible bronchoconstriction associated with chronic obstructive pulmonary disease, bronchial asthma, chronic bronchitis and related bronchospastic disorders.

Contraindications: Hypersensitivity to xanthines; active peptic ulcer in coronary artery disease when myocardial stimulation might prove harmful.

Warnings: Children: Parents should be cautioned against overdosing children; children are very sensitive to xanthines, especially to their CNS stimulant action. The margin of safety above therapeutic doses is small.

For once-a-day dosage forms, dosage has not been established for children up to 12 years of age.

Precautions: There is a marked variation in blood concentrations achieved in different patients given the same dose of theophylline which may lead to serious adverse effects in some patients. It is advisable to individualize dosage regimens. Ideally, all individuals should have serum theophylline concentrations measured. Theophylline clearance is decreased in certain situations which can lead to toxicity: in premature or neonatal infants; in patients over 60 years old; if the intake of carbohydrates is high; if there is concurrent methylxanthine intake; where drug interactions are present (see Table III); where the patient has concurrent disease such as, hepatic cirrhosis congestive heart failure, acute pulmonary edema, chronic obstructive lung disease, pneumonia, severe pulmonary obstruction, acute febrile episodes.

Table II	
Drug Interactions	
Interacting drug	Outcome / Mechanism
Cimetidine*	These drugs may increase serum theophylline concentrations.
Erythromycine* Ciprofloxacin* Allopurinol (large doses) Corticosteroids Mexiletine Propranolol Ticlopidine Verapamil	These drugs have potential to inhibit or impair hepatic metabolism of theophylline, decreasing its clearance.
Tobacco* Marijuana* Phenytoin ⁻ Phenobarbital Rifampin Aminoglutethimide Carbamazepine ⁻ Ketoconazole ⁻	These drugs may decrease serum theophylline concentrations.
Sympathomimetics i.e. Ephedrine Isoproterenol	These drugs have the potential to augment hepatic metabolism of theophylline, thereby increasing its clearance.
	The combination of theophylline and ephedrine has resulted in synergistic toxicity but no clinically significant increase in bronchodilatory effect.
Digoxin	Enhanced toxic potential of digoxin. Theophylline may enhance cardiac sensitivity to digoxin.
Lithium	Decreased serum concentration of lithium. Theophylline increases the excretion of lithium. Lithium levels should be followed.

* Interaction is of major clinical significance.

– In some cases serum concentrations of either or both drugs may be reduced.

Pregnancy: Although safe use of theophylline during pregnancy has not been established relative to the potential risk to the fetus, the drug has been used during pregnancy without teratogenicity or other adverse fetal effect; because of the risk of uncontrolled asthma, its safety during pregnancy when clearly needed is generally not seriously questioned.

Lactation: Theophylline is excreted in breast milk. May occasionally induce irritability or other signs of toxicity in nursing infant.

Adverse Effects: Theophylline toxicity is frequently related to large doses and high plasma concentrations of theophylline; severe effects are at concentrations below 110 µmol/L. Side effects most frequently experienced include; anorexia, nausea, vomiting, headache, abdominal discomfort, nervousness, insomnia, irritability. Tolerance to these effects may develop with continued dosing or a small reduction in dosage may alleviate the symptoms.

Atrial and ventricular arrhythmias may occur with serum theophylline concentrations greater than 110 µmol/L, or at therapeutic concentrations in patients with heart disease. Focal or generalized seizures have occurred over 222 µmol/L, as well as with lower concentrations. Toxicity of theophylline and its derivatives may present as follows:

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal cramps, epigastric pain, anorexia, reactivation of peptic ulcer, intestinal bleeding.

CNS: Headache, nervousness, insomnia, dizziness, lightheadedness, excitement, irritability, restlessness, fever, convulsions.

Cardiovascular: Palpitation, sinus tachycardia, atrial or ventricular arrhythmias, increased pulse rate, peripheral vascular constriction and/or collapse.

Urinary tract: Albuminuria.

Skin: Rarely urticaria, generalized pruritus, angioneurotic edema, contact dermatitis.

Blood: Very rarely bone marrow suppression, leucopenia, thrombocytopenia, hemorrhagic diathesis.

Miscellaneous: Proctitis has followed rectal theophylline administration.

I.V. injections must be given slowly and cautiously, especially in patients with pronounced myocardial injury. Rapid I.V. injection may cause sudden and profound hypotension.

Overdose: Symptoms: Children are more susceptible to toxicity. Seizures and death have occurred following large overdoses without prior symptoms of toxicity, this occurs more frequently in children. The most consistent reactions observed with toxic overdoses of theophylline are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.

CNS: In addition to those cited above, the patient may exhibit hyperreflexia, fasciculations and tonic-clonic convulsions.

Cardiovascular: As above, fatal arrhythmia or shock; marked hypotension and circulatory failure may be manifest.

Respiratory: Tachypnea and respiratory arrest may occur.

Renal: Albuminuria and microhematuria may occur. Increased excretion of renal tubular cells has been observed.

General Systemic Events: Syncope, collapse, fever and dehydration.

Treatment: If the drug is being given for therapeutic indications, discontinue administration. Multiple doses of activated charcoal may speed elimination whether theophylline was given orally or I.V. Repeat activated charcoal every 6 hours until serum, level is within the therapeutic range, some references suggest repeating charcoal at more frequent intervals. Support cardiac and respiratory functions as needed. Maintain fluid and electrolyte balance. Monitor ECG and treat arrhythmias.

Convulsions may be treated with diazepam. If diazepam is ineffective, phenytoin or phenobarbital may be used. Charcoal hemoperfusion and hemodialysis are effective in removing theophylline. Hemoperfusion is more effective than hemodialysis.

Dosage: Theophylline has a low therapeutic index; therefore, cautious dosage determination is essential. Individuals metabolize theophylline at different rates, appropriate dosages must be determined for each patient by carefully monitoring patient response and tolerance, pulmonary function and serum theophylline concentration. Dosage adjustments are based on clinical response with careful monitoring for manifestations of toxicity. Symptoms of toxicity may even occur when serum concentrations are within the upper end of the therapeutic range (85 to 110 µmol/L), particularly during initiation of therapy.

All dosages should be calculated from **lean** or **ideal** body weight.

Regardless of the salt used, dosages should be based on equivalent anhydrous theophylline content. Anhydrous aminophylline contains 86% of theophylline.

Acute: The loading dose does not have to be altered in disease states. The following loading doses are designed to achieve serum theophylline concentrations at the lower end of the therapeutic range (55 to 65 µmol/L).

If it has been established that the patient has not taken any theophylline preparation within the preceding 24 hours, the following loading dose is appropriate:

Load: Theophylline 5 mg/kg I.V. over 20 to 30 minutes (Aminophylline 6 mg/kg I.V. over 20 to 30 minutes).

If there is a strong suspicion that the patient has ingested some form of theophylline within the last 24 hours, then ideally, the loading dose should be deferred until a serum theophylline determination is made. Since this is usually not possible, proceed with caution and consider the use of other non-xanthine bronchodilators. If there is sufficient respiratory distress to warrant a small risk, a partial load may be administered.

Partial Load: Theophylline 2.5 mg/kg I.V. over 20 to 30 minutes (Aminophylline 3 mg/kg I.V. over 20 to 30 minutes).

This dose should produce a serum theophylline concentration of approximately 25 to 30 µmol/L greater than the existing serum concentration.

Alternatively, a dosage of 1 mg/kg for every desired 10 µmol/L increase in serum theophylline concentration may be used at the discretion of the clinician.

Maintenance: These recommendations are not designed to replace serum theophylline concentrations as a guide for dosage adjustment, and should be used only until serum concentrations are available (see Table III).

Table III		
Group	Dose of Theophylline I.V. (mg/kg/h)*	Aminophylline I.V. (mg/kg/h)*
Children 6 months to 9 years	0.79	1.0
Children 9 to 16 years and adults, otherwise healthy, smoker	0.63	0.8
Adults, otherwise healthy, nonsmoker	0.39	0.5
Geriatrics (>60 years) and patients with cor pulmonate	0.24	0.3
Patients with cardiac decompensation and/or significant liver disease	0.08 to 0.16	0.1 to 0.2

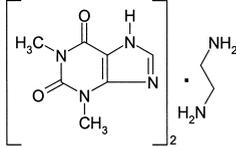
* Doses are designed to achieve a serum concentration of 55 µmol/L in most patients. Lean body weight should be used in obese patients.

The infusion is most accurately given by a constant infusion pump, but a minidrip set is adequate for clinical use if carefully adjusted.

Description:

Aminophylline, a xanthine bronchodilator, is a 2:1 complex of theophylline anc ethylenediamine and has the chemical name 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione.

The structural formula of aminophylline is as follows:



Presentation and availability:

Aminophylline Injection USP 25 mg/mL:

Each mL of solution contains 25 mg of aminophylline (equivalent to 21.4 mg anhydrous theophylline). Osmolarity of solution is 0.18 mOsmol/mL and pH between 8.6 and 9.0.

Aminophylline Injection USP 50 mg/mL:

Each mL of solution contains 50 mg of aminophylline (equivalent to 42.9 mg anhydrous theophylline). Osmolarity of solution is 0.36 mOsmol/mL and pH between 8.6 and 9.0.

General: Both presentations, protected with nitrogen, are available in 10-mL format, which do not contain any preservative agent. The unused portion should be discarded. Store between 15 and 30°C, protected from light.

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