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AMINOPHYLLINE

INJECTION

Composition

Each ampoule of 10 ml contains:

Active Ingredient

Aminophylline dihydrate 250 mg

Other Ingredient

Water for injection.

Mechanism of Action

Aminophylline is a soluble compound of theophylline with ethylenediamine.

The main action of theophylline is a direct relaxation of the smooth muscles of the bronchial airways and pulmonary blood vessels, thus acting as a bronchodilator.

It has also been demonstrated that aminophylline has a potent effect on diaphragmatic contractility in normal persons and may then be capable of reducing fatigability and therapy improve contractility in patients with chronic obstructive airway disease. The exact mode of action remains unsettled. Although theophylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP, other agents similarly inhibit the enzyme producing a rise of cyclic AMP but are unassociated with any demonstrable bronchodilation. Other mechanisms proposed include an effect on translocation of intracellular calcium, prostaglandin antagonism, stimulation of catecholamines endogenously, inhibition of cyclic guanosine monophosphate metabolism and adenosine receptor antagonisms. None of these mechanisms has been proved.

In vitro, theophylline has been shown to act synergistically with beta agonists and there is now available data which demonstrates an additive effect *in vivo* with combined use.

Theophylline also manifests other actions typical of the xanthine derivatives such as coronary vasodilation and diuresis.

Indications

For symptomatic relief or prevention of bronchial asthma and for treatment of reversible bronchospasm associated with chronic bronchitis and emphysema.

Contraindications

Known hypersensitivity to theophylline or to other xanthine derivatives.

It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

Aminophylline should not be administered concomitantly with other xanthine drugs. When therapeutic doses of aminophylline and/or theophylline are administered simultaneously by more than one route or in more than one preparation, the hazard of serious toxicity is increased.

Aminophylline Injection is contraindicated in patients with coronary artery disease where myocardial stimulation might prove harmful.

Aminophylline Injection is contraindicated in patients with bronchiolitis (bronchopneumonia).

The use of aminophylline is contraindicated in patients with acute porphyria.

Warnings

To reduce the undesirable stimulating effects of aminophylline on the central nervous and cardiovascular systems, intravenous administration of the drug should be slow and should not exceed a rate of 25 mg/min.

Aminophylline has a narrow therapeutic index and serum levels should be monitored regularly, particularly during initiation of therapy.

Aminophylline injection should be administered cautiously to patients over 55 years of age.

Elderly patients or those with cardiac or hepatic disease should be monitored carefully for signs of theophylline toxicity.

Care should be taken in patients undergoing influenza immunisation or who have active influenza infection or acute febrile illness.

Aminophylline should be given with caution to patients with cardiac failure, chronic obstructive pulmonary disease, renal or hepatic dysfunction and in chronic alcoholism since clearance of aminophylline is decreased.

During regular therapy serum potassium levels must be monitored. This is essential during combination therapy with β -2 agonists, corticosteroids or diuretics, or in the presence of hypoxia.

Aminophylline should be used with caution in patients with peptic ulcer, hyperthyroidism, glaucoma, diabetes mellitus, severe hypoxaemia, hypertension and compromised cardiac or circulatory function, as these conditions may be exacerbated.

Methylxanthines may increase gastric acidity and care should be taken when they are used in patients with a history of peptic ulceration.

Aminophylline should not be administered concurrently with other xanthine medications.

Excessive theophylline doses may be associated with toxicity. The determination of serum theophylline levels is mandatory to assure maximal benefit without excessive risk. The margin between therapeutic and toxic plasma levels is narrow so adverse events may easily occur; plasma levels should be monitored. Incidence of toxicity increases at serum theophylline levels greater than 20 micrograms/ml. Patients on oral theophylline preparations must have their plasma level measured prior to administration of I.V. aminophylline.

Concurrent Illness:

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

- Active peptic ulcer disease
- Seizure disorders
- Cardiac arrhythmias (not including bradyarrhythmias)

Conditions That Reduce Theophylline Clearance (and hence toxicity may be more likely):

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

- Age: premature or neonatal infants, children < 1 year, elderly (> 60 years)
- Concurrent Diseases: acute pulmonary edema or pneumonia, patients with congestive heart failure, cor pulmonale, acute febrile illness, chronic alcoholism, chronic obstructive pulmonary disease, influenza or those undergoing influenza immunization, hypothyroidism, liver disease; cirrhosis, acute hepatitis, reduced renal function in infants < 3 months of age, sepsis with multi-organ failure, shock.
- Cessation of Smoking
- Drug Interactions: adding a drug that inhibits theophylline metabolism (e.g., cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (e.g., carbamazepine, rifampin). (See also Precautions, and Drug Interactions, Table I.)

When Signs or Symptoms of Theophylline Toxicity Are Present:

Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), the intravenous infusion should be stopped and a serum theophylline concentration measured immediately.

Dosage Increases:

Increases in the dose of intravenous theophylline should not be made in response to an acute exacerbation of symptoms unless the steady-state serum theophylline concentration is <10 mcg/mL.

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

High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestations of toxicity in patients with lowered body plasma clearance, patients with liver dysfunction or chronic obstructive lung disease, patients who are older than 55 years of age, particularly males, those with cardiac failure from any cause, patients with sustained high fever, neonates and infants under 1 year of age, and those patients taking certain drugs (see Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug. Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Patients manifesting a decrease in total body theophylline clearance rate, include those patients with generalized debility, and acute hypoxias.

Many patients who have high theophylline serum levels exhibit tachycardia. Theophylline products may worsen preexisting arrhythmias.

Use in Pregnancy

Safe use in pregnancy has not been established. Since xanthines may cross the placental barrier possibly resulting in potentially dangerous serum xanthine levels in the neonate, risk-benefit must be considered when this drug is used in pregnancy.

The pharmacokinetics of aminophylline may be altered during pregnancy, and therefore serum theophylline concentrations may need to be measured more frequently in patients undergoing aminophylline therapy during pregnancy.

Animal reproduction studies have not been performed with theophyllines. It is not known whether theophyllines can cause fetal harm when administered to pregnant women. Although the safe use of theophylline during pregnancy has not been established relative to potential risk to the foetus, theophyllines have been used during pregnancy without teratogenicity or other adverse fetal effect

Use During Lactation

Since theophylline is excreted in breast milk (in concentrations about equivalent to the maternal serum concentrations: an infant ingesting a liter of breast milk containing 10 - 20 mcg/mL of theophylline per day is likely to receive 10 - 20 mg of theophylline per day), and breastfed infants may exhibit irritability and other side effects, use of theophylline is not recommended in nursing mothers.

Use in Pediatrics

Infants

Due to marked variation in theophylline metabolism in infants less than six months of age, use is not recommended in this age group. Drug elimination may be prolonged in premature infants and neonates.

Children

Children have a marked sensitivity to the CNS stimulant action of theophylline. This should be taken into consideration for proper dosage adjustment and monitoring.

Rapid intravenous injection is not recommended in children.

There have been reports of seizures in children with theophylline plasma levels within the accepted therapeutic range.

Alternative treatment should be considered in patients with a history of seizure activity and, if Aminophylline Injection is used in such patients, they should be carefully observed for possible signs of central stimulation.

Use in the Elderly

Elderly patients are at significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging.

Caution should be exercised when aminophylline is administered to patients older than 55 years of age. Theophylline clearance in healthy adults older than 60 years of age is 30% lower than healthy younger adults. These patients may require adjustment in dosage or dosing interval

Adverse Reactions

Adverse reactions are uncommon at serum theophylline levels below 20 micrograms/ml, although they may occasionally occur at a lower level.

At a serum level between 20-25 micrograms/ml, the adverse reactions usually experienced are nausea, vomiting, diarrhea, headache and insomnia.

At a level above 30 micrograms/ml, the adverse reactions that appear represent the symptoms of overdosage. These are, in addition to the above, hematemesis, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions, tachycardia, circulatory failure, life-threatening ventricular arrhythmia, tachypnea and albuminuria.

Immune system:

Hypersensitivity reactions (see also Skin and Appendages).

Cardiovascular System:

Tachycardia, palpitations, extrasystoles, increased pulse rate, flushing, hypotension, circulatory failure, atrial and ventricular arrhythmia, peripheral vasoconstriction.

Central Nervous System:

Headache, nervousness, insomnia, confusion, hyperventilation, irritability, restlessness, vertigo/dizziness, reflex hyperexcitability, seizures, anxiety, tremor, lightheadedness, excitement. Higher doses may lead to maniacal behavior, delirium and convulsions

Metabolism and nutrition disorders:

Metabolic disturbances such as hypokalaemia, hypophosphataemia, and hyponatraemia may occur.

Eye Disorders:

Visual disturbances.

Gastrointestinal System:

Nausea, vomiting, heartburn, epigastric pain, abdominal cramps, anorexia, diarrhea, gastroesophageal reflux, gastrointestinal bleeding, haematemesis.

Genitourinary:

Increased urination, albuminuria.

Respiratory System:

Tachypnea.

Skin and Appendages:

Ethylenediamine hypersensitivity induced dermatitis (hives, maculo-papular skin rash, erythema, pruritus, urticaria, exfoliative dermatitis, sloughing of skin).

General disorders and administration site conditions :

Intramuscular injections are painful, the pain lasting several hours.

Higher doses may result in hyperthermia and extreme thirst.

Other:

Fever.

Adverse reactions that may occur after too rapid intravenous administration:

Chest pain, decrease in blood pressure, dizziness, fast breathing, flushing, headache, pounding heartbeat, reaction to solution or administration technique (chills, fever, pain, redness or swelling at site of injection).

Adverse reactions whose incidence is rare:

Allergic reaction to ethylenediamine in aminophylline (skin rash or hives) {see also above}.

Note: These may not occur for 12 to 24 hours after initial administration.

Precautions

(see Warnings)

Theophylline should not be administered concurrently with other xanthine medications (see Contraindications).

This drug should be used with caution in patients with severe cardiac disease, compromised cardiac or circulatory functions, angina pectoris, acute myocardial injury (since myocardial stimulation would be harmful), severe hypoxemia, hypertension, hyperthyroidism, hypothyroidism, sepsis, seizure disorder, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, glaucoma, diabetes mellitus, tachyarrhythmias, in the elderly (particularly males) and in neonates. In particular, great caution should be used in giving theophylline to patients with congestive heart failure. Frequently, such patients have markedly prolonged theophylline serum levels.

Theophylline should be used cautiously in patients with gastritis or with a history of peptic ulcer.

Mean half-life in smokers is shorter than in nonsmokers, therefore smokers may require larger doses of theophylline.

Therapeutic doses of xanthines have been shown to induce gastroesophageal reflux when the patient is asleep or recumbent, thereby increasing the potential for aspiration which can aggravate bronchospasm; infants less than 2 years of age and elderly, debilitated, and stuporous patients with feeble gag and cough reflexes are especially susceptible to this effect.

Aminophylline Injection may lower the seizure threshold and should be administered with caution in patients with seizure disorder unless the patient is receiving appropriate anticonvulsant therapy. Dose adjustment of any anticonvulsant medication may be required.

Intravenous aminophylline must be administered slowly and cautiously to prevent dangerous CNS or cardiovascular toxicity. Too rapid intravenous administration may result in the following symptoms: anxiety, headache, nausea and vomiting, severe hypotension, dizziness, faintness, lightheadedness, palpitations, syncope, precordial pain, flushing, profound bradycardia, premature ventricular contractions, cardiac arrest.

Intramuscular administration is not recommended as it causes intense local pain (lasting for several hours) and sloughing of tissue.

The coagulation time of the blood is shortened with aminophylline therapy.

During regular therapy serum potassium levels must be monitored. This is essential during combination therapy with beta2-agonists, corticosteroids or diuretics (which possess hypokalemic effect), or in the presence of hypoxia.

Monitoring Serum Theophylline Concentrations:

General: Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy and prior to increases in theophylline dose

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

1. Before making a dose increase to determine whether the serum concentration is sub-therapeutic in a patient who continues to be symptomatic.
2. Whenever signs or symptoms of theophylline toxicity are present.
3. Whenever there is a new illness, worsening of an existing concurrent illness or a change in the patient's treatment regimen that may alter theophylline clearance (e.g., fever, hepatitis, or drugs listed in Table I are added or discontinued).

In patients who have received no theophylline in the previous 24 hours, a serum concentration should be measured 30 minutes after completion of the intravenous loading dose to determine whether the serum concentration is <10 mcg/mL indicating the need for an additional loading dose or >20 mcg/mL indicating the need to delay starting the constant I.V. infusion. Once the infusion is begun, a second measurement should be obtained after one expected half-life (e.g., approximately 4 hours in children 1 to 9 years and 8 hours in non-smoking adults). The second measurement should be compared to the first to determine the direction in which the serum concentration has changed. The infusion rate can then be adjusted before steady state is reached in an attempt to prevent an excessive or sub-therapeutic theophylline concentration from being achieved.

If a patient has received theophylline in the previous 24 hours, the serum concentration should be measured before administering an intravenous loading dose to make sure that it is safe to do so. If a loading dose is not indicated (i.e., the serum theophylline concentration is ≥ 10 mcg/mL), a second measurement should be obtained as above at the appropriate time after starting the intravenous infusion. If, on the other hand, a loading dose is indicated for guidance on selection of the appropriate loading dose), a second blood sample should be obtained after the loading dose and a third sample should be obtained one expected half-life after starting the constant infusion to determine the direction in which the serum concentration has changed.

Once the above procedures related to initiation of intravenous theophylline infusion have been completed, subsequent serum samples for determination of theophylline concentration should be obtained at 24-hour intervals for the duration of the infusion. The theophylline infusion rate should be increased or decreased as appropriate based on the serum theophylline levels.

When signs or symptoms of theophylline toxicity are present, the intravenous infusion should be stopped and a serum sample for theophylline concentration should be obtained as soon as possible, analyzed immediately, and the result reported to the clinician without delay. In patients in whom decreased serum protein binding is suspected (e.g., cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6-12 mcg/mL.

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

Drug Interactions

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

The drugs listed in Table I have the potential to produce clinically significant pharmacodynamic or pharmacokinetic interactions with theophylline. The information in the "Effect" column of Table I assumes that the interacting drug is being added to a steady-state theophylline regimen. If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (e.g., cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller.

Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (e.g., rifampin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

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

The listing of drugs in Tables I and II are not conclusive. New interactions are continuously being reported for theophylline, especially with new chemical entities. The clinician should not assume that a drug does not interact with theophylline if it is not listed in Table I. Before addition of a newly available drug in a patient receiving theophylline, the package insert of the new drug and/or the medical literature should be consulted to determine if an interaction between the new drug and theophylline has been reported.

Table I. Clinically Significant Drug Interactions With Theophylline*

Drug	Type of Interaction	Effect**
Adenosine	Theophylline blocks adenosine receptors.	Higher doses of adenosine may be required to achieve desired effect.
Alcohol	A single large dose of alcohol (3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase
Allopurinol	Decreases theophylline clearance at allopurinol doses \geq 600 mg/day.	25% increase
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease
Carbamazepine	Similar to aminoglutethimide.	30% decrease
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase
Ciprofloxacin	Similar to cimetidine.	40% increase
Clarithromycin	Similar to erythromycin.	25% increase
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.

Table I. Clinically Significant Drug Interactions With Theophylline*-continued

Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation and demethylation.	50% increase
Enoxacin	Similar to cimetidine.	300% increase
Ephedrine	Synergistic CNS effects.	Increased frequency of nausea, nervousness, and insomnia.
Erythromycin	Erythromycin metabolite decreases theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.
Estrogen	Estrogen containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine. The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines, theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase
Isoproterenol (I.V.)	Increases theophylline clearance.	20% decrease
Ketamine	Pharmacologic	May lower theophylline seizure threshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased an average of 60%.
Lorazepam	Similar to diazepam.	Similar to diazepam.

Methotrexate (MTX)	Decreases theophylline clearance.	20% increase after low dose MTX, higher dose MTX may have a greater effect.
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Mexiletine	Similar to disulfiram.	80% increase
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Table I. Clinically Significant Drug Interactions With Theophylline*-continued

Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease
Pancuronium	Theophylline may antagonize nondepolarizing neuromuscular blocking effects; possibly due to phosphodiesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after two weeks of concurrent Phenobarbital.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline and phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. Beta- ₂ blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. Beta-2 blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20 - 40% decrease
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase
Thiabendazole	Decreases theophylline clearance.	190% increase
Ticlopidine	Decreases theophylline clearance.	60% increase
Troleandomycin	Similar to erythromycin.	33 - 100% increase depending on troleandomycin dose.

Verapamil Similar to disulfiram. 20% increase

* Refer to Drug Interactions for further information regarding table.

** Average effect on steady-state theophylline concentration or other clinical effect for pharmacologic interactions. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

Table II. Drugs That Have Been Documented Not To Interact With Theophylline Or Drugs That Produce No Clinically Significant Interaction With Theophylline*

albuterol, systemic and inhaled	lomefloxacin
amoxicillin	mebendazole
ampicillin, with or without sulbactam	medroxyprogesterone
atenolol	methylprednisolone
azithromycin	metronidazole
caffeine, dietary ingestion	metoprolol
cefaclor	nadolol
co-trimoxazole (trimethoprim and sulfamethoxazole)	nifedipine
diltiazem	nizatidine
dirithromycin	norfloxacin
enflurane	ofloxacin
famotidine	omeprazole
felodipine	prednisone, prednisolone
finasteride	ranitidine
hydrocortisone	rifabutin
isoflurane	roxithromycin
isradipine	sorbitol (purgative doses do not inhibit theophylline absorption)
influenza vaccine	sucralfate
ketoconazole	terbutaline, systemic
	terfenadine
	tetracycline
	tocainide

* Refer to Drug Interactions for information regarding table.

The Effect of Other Drugs on Theophylline Serum Concentration Measurements:

Most serum theophylline assays in clinical use are immunoassays which are specific for theophylline. Other xanthines such as caffeine, dyphylline, and pentoxifylline are not detected by these assays. Some drugs (e.g., cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal dysfunction may cause the reading from some dry reagent office methods to be higher than the actual serum theophylline concentration.

Other Drug Interactions

Theophylline/Cigarette and Marijuana Smoking: Cigarette and marijuana smoking induce hepatic metabolism of theophylline. Smokers may therefore require a 50%-100% increase in dosage.

Theophylline/St. John's Wort (*Hypericum perforatum*): Plasma concentration of theophylline can be reduced by concomitant use of the herbal remedy St John's Wort (*Hypericum perforatum*).

Theophylline/Nicotine Chewing Gum/Other Smoking Deterrents/Cessation of Tobacco Smoking: Smoking cessation may increase the therapeutic effects of the xanthines (except dyphylline) by decreasing metabolism, thereby increasing their serum concentrations; however, after cessation of smoking, normalization of theophylline's pharmacokinetics may not occur for 3 months to 2 years, dosage adjustments may be necessary.

Theophylline/ Digitalis: Theophylline may enhance the sensitivity to and toxicity of digitalis.

Theophylline/ Oral Anticoagulants: Higher than usual doses may increase the effect of oral anticoagulants.

Theophylline/ Reserpine: Administration of theophylline with reserpine can cause tachycardia.

Theophylline/Fluconazole/Zafirlukast: These drugs may increase plasma theophylline concentrations.

Theophylline/Ritonavir: Plasma theophylline concentrations may be decreased.

Other Drug Interactions

Drugs that may decrease aminophylline clearance resulting in increased plasma theophylline concentrations and the potential for increased toxicity.

Quinolone antibiotics

Fluconazole

Isoniazid

Oral contraceptives

Zafirlukast

Thyroid hormones

Drugs that may decrease plasma theophylline concentrations

Ritonavir

Other Interactions

Xanthines: Concurrent use of other xanthine derivatives, including theophylline and pentoxifylline are contraindicated due to the risk of toxicity.

Benzodiazepines: Theophylline may reduce the effects of benzodiazepines.

Quinolones: Increased risk of convulsions.

General anaesthetics: Increased risk of convulsions with ketamine; increased risk of arrhythmias with halothane.

Pancuronium: Resistance to neuromuscular block with pancuronium has been reported in patients receiving aminophylline.

Sympathomimetics: Aminophylline may exhibit synergistic toxicity with ephedrine and other sympathomimetics and concurrent use may dispose the patient to cardiac arrhythmias.

β₂-adrenergic agonists: Increased risk of cardiac arrhythmias

β-blockers: Antagonism of bronchodilator effects.

Cardiac glycosides: The direct stimulatory effect of aminophylline on the myocardium may enhance the sensitivity and toxic potential of the cardiac glycosides.

Adenosine: The anti-arrhythmic effect of adenosine is antagonised by theophylline.

Leukotriene antagonists: In clinical trials co-administration with theophylline resulted in decreased plasma levels of zafirlukast, by approximately 30%, but with no effect on plasma theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered zafirlukast.

Doxapram: Increased CNS stimulation.

Hypokalaemia:

The hypokalaemic effects of β 2-adrenergic agonists may be potentiated by concomitant treatment with aminophylline.

There is an increased risk of hypokalaemia when theophylline derivatives are given with corticosteroids or diuretics

Drug/Food Interactions

Theophylline elimination is increased by a low carbohydrate, high protein diet and charcoal boiled foods. Conversely, the elimination is decreased by a high carbohydrate low protein diet.

Diagnostic Interference

When spectrophotometric methods are used, plasma theophylline concentrations may be falsely increased by coffee, tea, cola beverages, chocolate and paracetamol.

When high pressure liquid chromatography (HPLC) method is used, plasma theophylline concentrations may be falsely increased by caffeine, some cephalosporins and sulfa medications.

Theophylline/Dipyridamole-Assisted Myocardial Perfusion Studies: The theophylline bronchodilators, reverse the effects of dipyridamole on myocardial blood flow, thereby interfering with the test results. Therefore 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.

Laboratory Tests

As a result of its pharmacological effects, theophylline at serum concentrations within the 10 - 20 mcg/mL range modestly increases plasma glucose (from a mean of 88 mg% to 98 mg%), uric acid (from a mean of 4 mg/dl to 6 mg/dl), free fatty acids (from a mean of 451 μ Eq/L to 800 μ Eq/L), total cholesterol (from a mean of 140 vs 160 mg/dl), HDL (from a mean of 36 to 50 mg/dl), HDL/LDL ratio (from a mean of 0.5 to 0.7), and urinary free cortisol excretion (from a mean of 44 to 63 mcg/24 hr). Theophylline at serum concentrations within the 10 - 20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after one week and 142 ng/dl after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method of predicting toxicity.

For such measurements, the serum sample should be obtained at the time of peak concentration, 1 or 2 hours after administration for immediate release products. It is important that the patient will not have missed or taken additional doses during the previous 48 hours and that dosing intervals will have been reasonably equally spaced.

Dosage adjustment based on serum theophylline measurements when these instructions have not been followed may result in recommendations that present risk of toxicity to the patient.

Uric acid serum determinations:

Aminophylline produces false-positive elevations of serum uric acid as measured by the Bittner or colorimetric methods, but not by the uricase method.

Dosage and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

Aminophylline Injection should be administered by the intravenous route.

Aminophylline Injection should always be well diluted and warmed to room temperature.

Acute Symptoms of Bronchospasm Requiring Rapid Attainment of Theophylline Serum Levels for Bronchodilation.

Status asthmaticus should be considered a medical emergency and defined as that degree of bronchospasm which is not rapidly responsive to usual doses of conventional bronchodilators. Optimal therapy for such patients frequently requires both *additional medication*, parenterally administered, and *close monitoring*, preferably in an intensive care setting.

Loading Dose

Adults: In patients not currently receiving theophylline products, a loading dose of 6 mg aminophylline/kg body weight should be infused at a rate not exceeding 25 mg/minute. The loading dose should be reduced in patients receiving any theophylline-containing product. Each 0.6 mg aminophylline/kg body weight will result in approximately 1 microgram/ml increase in serum theophylline concentration.

Children: Doses are proportionally smaller and should be determined according to the child's weight.

Maintenance Infusions

The maintenance infusion rates recommended for continuous intravenous infusion of aminophylline are set out in the table below.

Monitoring of serum theophylline concentrations is recommended to accurately maintain therapeutic concentrations and as a guide to dosage adjustments.

Aminophylline Maintenance Infusion Rates (mg/kg body weight/hr)

Patient Group	First 12 hours	Beyond 12 hours
Children 6 months- 9 years	1.2	1.0
Children 9-16 years and young adult smokers	1.0	0.8
Otherwise-healthy nonsmoking adults	0.7	0.5
Older patients and patients with cor pulmonale	0.6	0.3
Patients with congestive heart failure or liver disease	0.5	0.1-0.2

Overdosage

Manifestations

Less severe toxicities do not always precede major toxicities. Chronic overdose may produce toxicity at serum levels lower than those in acute overdose. Potentially life threatening toxicities may occur at serum concentration greater than 40 microgram/mL (220 micromole/L) in chronic overdose. In acute overdose serum concentrations greater than 90 microgram/mL (495 micromole/L) are generally associated with severe toxicity.

The following signs and symptoms may be present in aminophylline overdose:

- *cardiovascular*: tachycardia, arrhythmias, palpitations, hypotension.
- *central nervous system*: agitation, confusion or altered behaviour including toxic psychosis, seizures.
- *gastrointestinal*: nausea, vomiting, diarrhoea and/or hematemesis, continuing or severe abdominal pain, acute pancreatitis.
- *genitourinary*: renal failure.
- *metabolic*: hyperglycaemia, hypokalaemia, metabolic acidosis, hypophosphataemia, hypercalcaemia.
- *respiratory*: tachypnea, respiratory arrest, respiratory alkalosis.
- *other*: extreme thirst, slight fever, tinnitus.

Treatment

There is no specific antidote for aminophylline overdose. Treatment of overdose is symptomatic and supportive. Administration of sympathomimetic drugs should be avoided. Treatment may involve the following measures:

- administration of oral activated charcoal, regardless of the route of exposure to aminophylline (this assists in decreasing the serum concentration of theophylline by interrupting the enterohepatic circulation). Oral activated charcoal should be repeated until the serum theophylline concentration is below 20 microgram/mL.
- charcoal hemoperfusion to increase the elimination of aminophylline. Hemodialysis is less effective in eliminating aminophylline, but may be warranted in some patients.
- administration of intravenous diazepam to control seizures. Where diazepam is ineffective, phenytoin, phenobarbitone, or thiopentone may be considered.
- correction of fluid and electrolyte balance.
- support of respiratory functions by airway management, oxygen administration or mechanical ventilation as required.
- support of cardiac functions. Propranolol may be warranted in the presence of extreme tachycardia, and antiarrhythmic therapy may be required.
- administration of phenothiazines in the presence of life threatening hypothermia.
- monitoring of serum theophylline concentrations and ECG.

Pharmaceutical Precautions

Do not use Aminophylline Injection if the crystals are present. Although there have been reports of aminophylline precipitating in acidic media, these reports do not apply to the dilute solutions found in IV infusions. Aminophylline Injection should not be mixed in a syringe with other drugs but should be added separately to the IV solution.

When an IV solution containing aminophylline is given "piggyback", the IV system already in place should be turned off while the aminophylline is infused if there is a potential problem with admixture incompatibility.

Aminophylline is reported to be incompatible with the following drugs:

Strong acid solutions, ascorbic acid, corticotrophin, adrenaline, amiodarone, ascorbic acid, benzylpenicillin, chlorpromazine hydrochloride, ciprofloxacin, clindamycin, codeine phosphate, diltiazem, dimenhydrinate, dobutamine, doxapram, doxorubicin, erythromycin gluceptate, hydralazine, hydroxyzine HCl, insulin, methadone HCl, methicillin sodium, morphine sulfate, noradrenaline acid tartrate, opioid analgesics, oxytetracycline hydrochloride, penicillin G potassium, pentazocine lactate, pethidine HCl, (meperidine) phenobarbitone sodium, phenytoin sodium, potassium, prochlorperazine edisylate, procaine hydrochloride, promazine hydrochloride, promethazine hydrochloride, ondansetron, sulphafurazole diethanolamine, tetracycline hydrochloride, vancomycin hydrochloride, vitamin B complex with C.

Aminophylline containing solutions are alkaline, and hence drugs known to be alkali labile should not be added to aminophylline containing solutions.

Storage

Store below 25°C.

Drug Registration No.: 063 85 22594 21

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