

Methylxanthines

Purine-derived drugs, theophylline chief among them, that relax airway smooth muscle and stimulate respiration but are defined in practice by a narrow therapeutic index, obligatory serum concentration measurement, and a clearance that shifts with illness, age, smoking and a long list of co-prescribed medicines.

Online guide: <https://www.medguideglobal.com/pharmacology/respiratory-and-allergy/methylxanthines>

Content updated: 2026-08-23

Quick revision

One Liner: Everything difficult about this class follows from one fact: the concentration that helps and the concentration that harms are close together, and clearance varies fourfold between otherwise similar patients.

1. The theophylline label places bronchodilation over a serum concentration range of 5 to 20 mcg/mL, and states that above 20 mcg/mL both the frequency and the severity of adverse reactions increase. [1]
2. Its label is candid that the mechanisms of action are not known with certainty, and attributes bronchodilation in animal studies to inhibition of phosphodiesterase III and, to a lesser extent, IV. [1]
3. Some adverse effects are attributed to phosphodiesterase III inhibition, including hypotension, tachycardia, headache and emesis, and others to adenosine receptor antagonism. [1]
4. Clearance falls by half or more in congestive heart failure and in hepatic insufficiency such as cirrhosis, acute hepatitis or cholestasis, and sustained fever also reduces it. [1]
5. Tobacco smoking raises clearance by roughly 50% in young adults and 80% in elderly smokers, and one week of abstinence lowers it by about 40%, so quitting can push a stable patient into toxicity. [1]
6. Theophylline is demethylated by cytochrome P-450 1A2, which is why cimetidine, ciprofloxacin and fluvoxamine all raise its concentration, and why rifampin and carbamazepine lower it. [1]
7. Aminophylline is a 2:1 complex of theophylline and ethylenediamine, about 79% anhydrous theophylline by weight, given by slow intravenous injection or by infusion. [2]
8. Caffeine citrate is the methylxanthine of the neonatal unit, indicated for short-term treatment of apnoea of prematurity in infants between 28 and under 33 weeks gestational age. [3]
9. Above 20 mcg/mL theophylline produces persistent vomiting, cardiac arrhythmias and intractable seizures which the label states can be lethal. [1]

Overview

1. Methylxanthines are purine derivatives that relax bronchial smooth muscle and stimulate the respiratory centre. Theophylline is the member that matters most in respiratory medicine, aminophylline is the intravenous form of the same active moiety, and caffeine citrate occupies a separate niche in neonatal apnoea. What unites them pharmacologically is a modest and slowly achieved bronchodilator effect purchased at the cost of a therapeutic range that sits immediately below a toxic one. [1][2][3]
2. The label states that the pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight or other demographic characteristics, and that the amount required to reach a peak concentration in the 10 to 20 mcg/mL range varies fourfold among otherwise similar adults. There is, in the label's words, no single theophylline dose that will provide both safe and effective serum concentrations for all patients in a given population. Measurement of the serum concentration is therefore not an optional refinement; it is how the drug is used at all. [1]
3. The second defining feature is interaction burden. Theophylline is metabolised principally by cytochrome P-450 1A2, so anything that inhibits or induces that pathway moves the concentration, and the label warns that discontinuation of a

drug that increases theophylline clearance will result in accumulation to potentially toxic levels unless the theophylline dose is appropriately reduced. Smoking status behaves like a drug interaction in this respect. Because inhaled beta-2 selective agonists and systemically administered corticosteroids are described in the aminophylline label as the treatments of first choice in acute asthma exacerbations, the class now sits behind inhaled therapy rather than alongside it. [1][2]

Classification and drug examples

Intro: A small class, best divided by which xanthine is involved and what it is being asked to do. Theophylline and its salts are the airway drugs; caffeine belongs to the neonatal unit; and pentoxifylline is included because it is chemically a xanthine and shares the class hypersensitivity, yet does nothing for the airway.

1. Name: Theophylline and its salts

1. Note: The same active moiety in two presentations, oral for maintenance and intravenous for the ward. Serum concentration measurement governs both.

1. Name: Theophylline

Anhydrous theophylline

1. Route: Oral, including extended-release formulations

1. Note: Structurally classified in its label as a methylxanthine. Extended-release tablets are recommended for chronic or long-term management and prevention of symptoms, and not for treating acute symptoms of asthma and reversible bronchospasm. [1]

2. Name: Aminophylline

Theophylline ethylenediamine

2. Route: Slow intravenous injection or intravenous infusion

2. Note: A 2:1 complex of theophylline and ethylenediamine, approximately 79% anhydrous theophylline by weight. The ethylenediamine component carries its own hypersensitivity risk that plain theophylline does not. [2] [1][2]

2. Name: Caffeine and its salts

2. Note: The neonatal member of the class, used as a respiratory stimulant rather than as a bronchodilator.

Name: Caffeine citrate

Route: Intravenous or oral solution

Note: Its label attributes most of the hypothesised effects in apnoea of prematurity to antagonism of adenosine receptors of both the A1 and A2 subtypes, demonstrated in receptor binding assays at concentrations approximating those achieved therapeutically. [3] [3]

3. Name: Xanthine derivatives used outside the airway

3. Note: Chemically part of the family, therapeutically nothing to do with bronchodilation. Worth knowing because the class hypersensitivity still applies.

Name: Pentoxifylline

Route: Oral, extended-release

Note: Described in its label as a tri-substituted xanthine derivative that, unlike theophylline, is a haemorrheologic agent affecting blood viscosity. It is contraindicated in patients who have previously shown intolerance to methylxanthines such as caffeine, theophylline and theobromine. [4] [4]

Mechanism of action

Summary: Two mechanisms are proposed and neither is presented by the labels as settled. Phosphodiesterase inhibition and adenosine receptor antagonism are both invoked, and the theophylline label goes further by stating that the non-bronchodilator prophylactic actions probably work through mechanisms that involve neither. A page that claims to know which one explains the clinical effect is claiming more than the regulatory text does.

Target: Phosphodiesterase isozymes III and IV, adenosine receptors including the A1 and A2 subtypes, and a diaphragmatic calcium uptake pathway

Cidal Static: Bronchodilator and respiratory stimulant; symptom-suppressing rather than disease-modifying

Kill Kinetics: Effect tracks the serum concentration, with benefit and toxicity separated by a narrow margin

1. Step: 1

1. Title: Two distinct actions in the airway

1. Detail: The label describes theophylline as having smooth muscle relaxation, that is bronchodilation, and suppression of the response of the airways to stimuli, described as non-bronchodilator prophylactic effects. These are treated as separate actions rather than two descriptions of one. [1]

2. Step: 2

2. Title: Phosphodiesterase inhibition, proposed rather than proven

2. Detail: While stating that the mechanisms of action are not known with certainty, the label reports that studies in animals suggest bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase, PDE III and, to a lesser extent, PDE IV. The non-bronchodilator prophylactic actions are said to be probably mediated through one or more different molecular mechanisms that do not involve inhibition of PDE III or antagonism of adenosine receptors. [1]

3. Step: 3

3. Title: Adenosine receptor antagonism

3. Detail: Theophylline blocks adenosine receptors, which is why the label warns that higher doses of adenosine may be required to achieve the desired effect when the two are used together. The caffeine citrate label attributes most of the proposed respiratory effects in apnoea of prematurity to antagonism of A1 and A2 adenosine receptors. [1][3]

4. Step: 4

4. Title: Mechanism explains part of the toxicity

4. Detail: Some of the adverse effects are attributed by the label to phosphodiesterase III inhibition, naming hypotension, tachycardia, headache and emesis, and others to adenosine receptor antagonism, naming alterations in cerebral blood flow. The unwanted effects are therefore extensions of the same pharmacology, not separate idiosyncrasies. [1]

5. Step: 5

5. Title: An effect on the respiratory muscles

5. Detail: Theophylline increases the force of contraction of diaphragmatic muscles, an action the label ascribes to enhancement of calcium uptake through an adenosine-mediated channel. In chronic obstructive pulmonary disease this shows up as reduced dyspnoea, less air trapping and reduced work of breathing with little or no improvement in pulmonary function measurements. [1]

Major clinical uses

1. Drug: Theophylline

1. Organism: Not applicable

1. Indication: Symptoms and reversible airflow obstruction of chronic asthma

1. Line: add-on maintenance

1. Note: Clinical studies cited in the label show reduced frequency and severity of symptoms including nocturnal exacerbations, and reduced as-needed use of inhaled beta-2 agonists, in patients with chronic asthma. [1]

2. Drug: Theophylline

2. Organism: Not applicable

2. Indication: Chronic lung diseases including emphysema and chronic bronchitis

2. Line: add-on maintenance

2. Note: In chronic obstructive pulmonary disease the demonstrated gains are symptomatic: less dyspnoea, less air trapping, reduced work of breathing and improved diaphragmatic contractility, with little or no change in spirometry. [1]

3. Drug: Aminophylline

3. Organism: Not applicable

3. Indication: Acute exacerbations of asthma and other chronic lung diseases, as an adjunct

3. Line: adjunctive, second line to inhaled therapy

3. Note: Its label positions intravenous theophylline as an adjunct to inhaled beta-2 selective agonists and systemically administered corticosteroids, and reports that trial results have been conflicting, with most emergency department studies showing no greater bronchodilation and an increased risk of adverse effects. [2]

4. Drug: Caffeine citrate

4. Organism: Not applicable

4. Indication: Short-term treatment of apnoea of prematurity

4. Line: established in neonatal care

4. Note: Indicated in infants between 28 and under 33 weeks gestational age. In the pivotal trial the percentage of patients without apnoea on day two of treatment was significantly greater with caffeine citrate than with placebo. [3]

5. Drug: Pentoxifylline

5. Organism: Not applicable

5. Indication: Intermittent claudication from chronic occlusive arterial disease of the limbs

5. Line: adjunct to definitive vascular treatment

5. Note: A xanthine with no airway indication. Its label states it can improve function and symptoms but is not intended to replace more definitive therapy such as surgical bypass or removal of arterial obstructions. [4]

Pharmacokinetics

1. Drug: Theophylline

1. Route: Oral

1. Absorption: Rapid and complete from solution or immediate-release solid dosage forms, with no appreciable pre-systemic elimination

1. Csf Penetration: Passes freely into cerebrospinal fluid, across the placenta and into breast milk

1. Metabolism: About 90% hepatic beyond the first year of life; demethylation by cytochrome P-450 1A2 and hydroxylation by 2E1 and 3A3

1. Elimination: Urinary, but only about 10% as unchanged drug in adults and children over three months

1. Half Life: Mean 8.7 hours in otherwise healthy non-smoking adult asthmatics, with a reported range of 6.1 to 12.8 hours

1. Dose Adjust: Both metabolic pathways are capacity-limited, so non-linearity may begin in some patients above 10 mcg/mL and changes are made in small increments [1]

2. Drug: Aminophylline

2. Route: Slow intravenous injection or infusion

2. Absorption: Not applicable; given intravenously

2. Csf Penetration: As for theophylline, since theophylline is the active moiety

2. Metabolism: Hepatic, as theophylline

2. Elimination: Hepatic, as theophylline

2. Half Life: As for theophylline, and highly variable with age and concurrent illness

2. Dose Adjust: Its label recommends that serum theophylline concentrations be measured frequently in acutely ill patients receiving intravenous theophylline, for example at 24-hour intervals [2]

3. Drug: Caffeine citrate

3. Route: Intravenous or oral

3. Absorption: Rapid oral absorption in preterm neonates, with peak concentrations reached within about 30 minutes to 2 hours

3. Csf Penetration: Rapidly distributed into the brain, with cerebrospinal fluid levels approximating plasma levels in preterm neonates

3. Metabolism: Cytochrome P-450 1A2, but limited in preterm neonates because of immature hepatic enzyme systems

3. Elimination: Largely renal in neonates, with about 86% excreted unchanged within six days

3. Half Life: Approximately 3 to 4 days in neonates, falling to about 5 hours by nine months of age
3. Dose Adjust: Caution in impaired renal or hepatic function, with serum caffeine concentrations monitored to avoid toxicity [3]
1. This page gives no dose regimens. Selection, titration, concentration monitoring and withdrawal of a methylxanthine rest with the treating clinician working from a current prescribing reference, because they turn on age, smoking status, concurrent illness and every other medicine the patient is taking.
2. The label directs that a serum concentration is measured when therapy is initiated, before any increase in a patient who remains symptomatic, whenever signs or symptoms of toxicity appear, and whenever a new illness or a change in the treatment regimen might alter clearance. [1]
3. Reduced protein binding in cirrhosis, in the third trimester, in the elderly and in premature neonates means a patient may show signs of toxicity while the total concentration still reads within range, and unbound concentrations are generally kept between 6 and 12 mcg/mL in that situation. [1]
4. Renal impairment is the exception that catches people out: because so little unchanged drug appears in the urine, no adjustment for renal insufficiency is required in adults and children over three months, while neonates excrete about half the dose unchanged and do need one. [1]

Adverse effects

1. Effect: Caffeine-like effects below 20 mcg/mL
1. Detail: Nausea, vomiting, headache and insomnia, described in the label as generally mild and transient at peak concentrations under 20 mcg/mL. They occur in about half of patients when therapy is started above the recommended initial amount, and persist during maintenance in under 3% of children and under 10% of adults. [1]
2. Effect: Neurological and gastrointestinal stimulation
2. Detail: Diarrhoea, irritability, restlessness, fine skeletal muscle tremors and transient diuresis are all reported at concentrations below 20 mcg/mL. Tremor and tachycardia are the findings students are expected to link back to the drug's stimulant pharmacology. [1]
3. Effect: Metabolic changes within the usual range
3. Detail: At concentrations of 10 to 20 mcg/mL the label records modest rises in plasma glucose, uric acid, free fatty acids and total cholesterol, and a transient fall in triiodothyronine. These are laboratory observations rather than symptoms, but they explain unexpected results in a monitored patient. [1]
1. Effect: Arrhythmia and seizure at toxic concentrations
1. Detail: Above 20 mcg/mL the label describes persistent vomiting, cardiac arrhythmias and intractable seizures which can be lethal. After chronic overdosage, generalised seizures, life-threatening cardiac arrhythmias and death may occur once concentrations exceed 30 mcg/mL.
1. Action: Serial concentrations, electrocardiographic monitoring and management of the arrhythmia or seizure belong to the treating team; the label directs that monitoring continues until the concentration falls below 20 mcg/mL. [1]
2. Effect: Toxicity without a warning symptom
2. Detail: Gastrointestinal upset is an unreliable herald. In the two chronic overdosage series tabulated in the label, 6% of patients with concentrations above 30 mcg/mL were asymptomatic, vomiting was recorded in only 30% and 61% of cases, and seizures occurred in 14% and 5%. Ventricular arrhythmias with haemodynamic instability were reported in 40% of one chronic series.
2. Action: The label instructs that whenever nausea or vomiting, particularly repetitive vomiting, or any other sign consistent with toxicity appears, further doses are withheld and a concentration measured immediately, even if another cause is suspected. [1]
3. Effect: Seizures that resist anticonvulsant treatment
3. Detail: Seizures associated with concentrations above 30 mcg/mL are described as often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death is most often secondary to cardiorespiratory arrest or hypoxic encephalopathy following prolonged generalised seizures or intractable arrhythmias.

3. Action: This is the reason the class is treated as a poisoning risk rather than a nuisance, and why concentration measurement is not deferred once symptoms appear. [1]
4. Effect: Toxicity inside the usual concentration range
4. Detail: Multifocal atrial tachycardia and flutter have been reported at concentrations around 15 mcg/mL in patients hypoxic from chronic obstructive pulmonary disease, and there are isolated reports of seizures below 20 mcg/mL in patients with underlying neurological disease or in the elderly, in whom reduced protein binding raises the active unbound fraction.
4. Action: A concentration inside the range does not exclude drug toxicity in a patient with cardiac or neurological disease, and the clinical picture governs. [1]
5. Effect: Hypokalaemia
5. Detail: Low serum potassium was among the commonest metabolic findings in theophylline toxicity, recorded in 85% and 79% of acute overdose cases and 44% and 43% of chronic overdosage cases in the two series tabulated. Inhaled beta-2 agonists, which are given alongside these drugs in acute asthma, may themselves produce significant hypokalaemia, possibly through intracellular shunting, with the potential to produce adverse cardiovascular effects.
5. Action: The theophylline label directs that serum electrolytes and glucose are measured on presentation in overdose and that fluid and electrolyte abnormalities are promptly corrected. [1][6]
1. Drug: Aminophylline
1. Effect: Reactions attributable to ethylenediamine rather than to theophylline: rarely severe allergic skin reactions including exfoliative dermatitis after systemic administration in a patient previously sensitised by a topical ethylenediamine-containing substance, and contact dermatitis in pharmacists and others who handle the drug repeatedly. [2]
2. Drug: Caffeine citrate
2. Effect: Necrotising enterocolitis occurred in six of the 85 infants in the controlled trial, three of them fatal, with five of the six exposed to caffeine citrate; the label states that a causal relationship between methylxanthine use and necrotising enterocolitis has not been established but directs careful monitoring. Hypoglycaemia and hyperglycaemia have both been observed. [3]
3. Drug: Pentoxifylline
3. Effect: Occasional reports of angina, hypotension and arrhythmia. Controlled trials do not show these occur more often than with placebo, but the label notes that as it is a methylxanthine derivative some individuals may experience such responses. [4]

Contraindications, precautions and interactions

1. Theophylline extended-release tablets are contraindicated in patients with a history of hypersensitivity to theophylline or to other components of the product. [1]
2. Aminophylline is contraindicated in patients with a history of hypersensitivity to theophylline or to other components including ethylenediamine, which widens the contraindication beyond that of oral theophylline. [2]
3. Pentoxifylline must not be used after recent cerebral or retinal haemorrhage, nor in a patient who has previously shown intolerance to methylxanthines such as caffeine, theophylline and theobromine. [4]
1. Extreme caution is directed in active peptic ulcer disease, in seizure disorders, and in cardiac arrhythmias other than bradyarrhythmias, because of the risk of making the concurrent condition worse. [1]
2. Named causes of reduced clearance in the label include acute pulmonary oedema, congestive heart failure, cor pulmonale, sepsis with multi-organ failure and shock, hypothyroidism, the third trimester of pregnancy, and fever at or above 102 degrees Fahrenheit sustained for 24 hours or more. [1]
3. The extremes of age carry the greatest risk: neonates, infants under one year and adults over 60. Elderly patients are described as at significantly greater risk of serious toxicity, and after chronic overdosage the severity correlates more strongly with age than with the peak concentration. [1]
4. If the total daily amount is not reduced when these risk factors are present, the label warns that severe and

potentially fatal theophylline toxicity can occur. [1]

1. With: Ciprofloxacin and other cytochrome P-450 1A2 inhibitors

1. Effect: Ciprofloxacin decreases theophylline clearance, an average 40% rise in the theophylline label. The ciprofloxacin label carries a capitalised warning that serious and fatal reactions have been reported with concurrent administration, including cardiac arrest, seizure, status epilepticus and respiratory failure, and directs that concentrations be monitored if the combination cannot be avoided. [1][5]

2. With: Cimetidine, fluvoxamine and other inhibitors of metabolism

2. Effect: Cimetidine decreases theophylline clearance by inhibiting cytochrome P-450 1A2, giving an average 70% increase in concentration; fluvoxamine behaves similarly. Enoxacin is listed with a 300% increase, thiabendazole 190%, tacrine 90%, and interferon alfa 100%. [1]

3. With: Rifampin, carbamazepine, phenobarbital and phenytoin

3. Effect: All increase clearance and lower the concentration: rifampin by 20 to 40%, carbamazepine by about 30%, phenobarbital by about 25% after two weeks. Phenytoin is bidirectional, with theophylline and phenytoin concentrations each falling by roughly 40%. [1]

4. With: Tobacco and cannabis smoking, and stopping smoking

4. Effect: Smoking induces the metabolic pathways, raising clearance by about 50% in young adult smokers and 80% in elderly smokers, and even passive exposure can raise it by up to 50%. Abstinence for one week reduces clearance by approximately 40%, so a patient who quits while stable is at risk of accumulation. [1][7]

5. With: Adenosine

5. Effect: Because theophylline blocks adenosine receptors, higher doses of adenosine may be required to achieve the desired effect. This is a pharmacodynamic antagonism, not a change in concentration. [1]

6. With: Halothane and propranolol

6. Effect: Halothane sensitises the myocardium to catecholamines while theophylline increases their release, giving an increased risk of ventricular arrhythmias. Propranolol raises the concentration by around 100% and its beta-2 blocking effect may in addition reduce theophylline's efficacy. [1]

7. With: Lithium

7. Effect: Theophylline increases renal lithium clearance; the lithium amount needed to reach a therapeutic concentration rose by an average of 60% in the data cited. [1]

8. With: St John's wort and dietary caffeine

8. Effect: St John's wort lowers theophylline concentrations, and the label warns that stopping it may result in toxicity unless this is anticipated. MedlinePlus separately advises against large amounts of coffee, tea, cocoa and chocolate during treatment because they may increase the drug's side effects. [1][7]

Comparison tables

Title: The four xanthines worth telling apart

Caption: Chemistry unites them; indication and monitoring separate them. Choice, monitoring interval and any change of treatment rest with the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: role

2. Label: Therapeutic role

3. Key: route

3. Label: Usual route

4. Key: monitoring

4. Label: Concentration monitoring

1. Drug: Theophylline

1. Role: Add-on bronchodilator and prophylactic agent in chronic asthma and COPD
1. Route: Oral, usually extended-release
1. Monitoring: Central to use; measured at initiation, before any increase, on symptoms of toxicity and on any change in clearance [1]
2. Drug: Aminophylline
2. Role: Intravenous adjunct in acute exacerbations, behind inhaled beta-2 agonists and corticosteroids
2. Route: Slow intravenous injection or infusion
2. Monitoring: Frequent measurement recommended in acutely ill patients, for example at 24-hour intervals [2]
3. Drug: Caffeine citrate
3. Role: Respiratory stimulant for apnoea of prematurity
3. Route: Intravenous or oral solution
3. Monitoring: A therapeutic range could not be determined from the controlled trial; serious toxicity has been reported above 50 mg/L [3]
4. Drug: Pentoxifylline
4. Role: Haemorrhagic agent for intermittent claudication, with no airway indication
4. Route: Oral, extended-release
4. Monitoring: Not concentration-guided; warfarin co-treatment prompts more frequent prothrombin time checks [4]

High-yield exam pearls

1. Pearl: Both metabolic pathways are capacity-limited, and non-linear elimination may begin in some patients above 10 mcg/mL, so changes in concentration can be more than proportional to the change in dose.
1. Why: It is the pharmacokinetic reason a patient can move from a comfortable concentration to a toxic one after a modest adjustment, and it is why the label advises small increments. [1]
2. Pearl: Smoking status is a drug interaction in disguise: clearance rises by roughly half in young adult smokers and four-fifths in elderly smokers, and falls by about 40% after a week without tobacco.
2. Why: The examinable scenario is a stable patient admitted to a smoke-free hospital who becomes toxic without any change to the prescription. [1]
3. Pearl: Most serum theophylline assays are immunoassays specific for theophylline, and other xanthines such as caffeine, dyphylline and pentoxifylline are not detected by them.
3. Why: It explains why a concentration cannot be used to monitor a different xanthine, and why neonatal samples behave oddly when caffeine accumulates. [1]
4. Pearl: Caffeine and theophylline interconvert in preterm neonates: caffeine concentrations run at roughly 25% of theophylline concentrations after theophylline, and about 3 to 8% of administered caffeine is expected to convert to theophylline.
4. Why: It is the reason the two neonatal xanthines cannot be treated as pharmacologically separate agents, and a favourite detail in neonatal pharmacology questions. [3]
5. Pearl: Renal impairment does not call for adjustment in adults or in children over three months, because only about 10% of the dose leaves as unchanged drug, whereas neonates excrete roughly half unchanged and do need it.
5. Why: It reverses the reflex that renal impairment always means reducing a dose, and the neonatal exception is the half that gets forgotten. [1]

Common exam traps

1. Trap: Reaching for a methylxanthine to treat an acute attack the way an inhaled reliever is used.
1. Correction: The label states that increases should not be made in response to an acute exacerbation of chronic lung disease, because theophylline adds little to inhaled beta-2 selective agonists and systemic corticosteroids in that setting while increasing the risk of adverse effects. [1]
2. Trap: Reading a concentration inside the quoted range as proof that the patient is not toxic.

2. Correction: Reduced protein binding in cirrhosis, late pregnancy, the elderly and premature neonates raises the active unbound fraction, and the label records arrhythmias around 15 mcg/mL in hypoxic COPD and isolated seizures below 20 mcg/mL. [1]
3. Trap: Expecting vomiting to announce toxicity before anything dangerous happens.
3. Correction: In the chronic overdosage series in the label, some patients above 30 mcg/mL were asymptomatic, vomiting was recorded in a minority to a bare majority of cases, and arrhythmia or seizure could be the presenting feature. [1]
4. Trap: Assuming every methylxanthine is a bronchodilator because of the shared purine skeleton.
4. Correction: Pentoxifylline is a tri-substituted xanthine derivative that its own label distinguishes from theophylline as a haemorrhagic agent affecting blood viscosity, indicated for intermittent claudication. [4]
5. Trap: Treating aminophylline and theophylline as interchangeable in every respect because the active moiety is the same.
5. Correction: Aminophylline carries the ethylenediamine component, which brings its own hypersensitivity contraindication and can cause contact dermatitis in people who handle the drug. [2]

Self-test questions

1. Question: A patient stable on oral theophylline is admitted and stops smoking. One week later he is nauseated, tremulous and tachycardic. What is the most likely explanation?
 1. Loss of smoking-induced enzyme activity has reduced theophylline clearance
 2. Nicotine withdrawal alone accounts for all of the findings
 3. Reduced gastrointestinal absorption has lowered the concentration
 4. Theophylline has begun to induce its own metabolism
1. Explanation: The label reports that abstinence from tobacco smoking for one week causes a reduction of approximately 40% in theophylline clearance, and directs careful attention to dose reduction and frequent monitoring of concentrations in patients who stop smoking. [1]
2. Question: Which statement best reflects what the theophylline label says about the drug's mechanism of action?
 1. The mechanisms are not known with certainty, with animal studies suggesting phosphodiesterase III and IV inhibition
 2. Bronchodilation is proven to result from adenosine A1 receptor antagonism
 3. The drug acts as a direct beta-2 adrenoceptor agonist on airway smooth muscle
 4. It works entirely through inhibition of leukotriene synthesis
2. Explanation: The label states that while the mechanisms of action are not known with certainty, studies in animals suggest that bronchodilation is mediated by inhibition of two isozymes of phosphodiesterase, PDE III and to a lesser extent PDE IV. [1]
3. Question: Which co-prescribed antibiotic carries a specific labelled warning about serious and fatal reactions when given with theophylline?
 1. Ciprofloxacin
 2. Amoxicillin
 3. Azithromycin
 4. Co-trimoxazole
3. Explanation: The ciprofloxacin label states in capitals that serious and fatal reactions have been reported with concurrent administration, including cardiac arrest, seizure, status epilepticus and respiratory failure, because ciprofloxacin inhibits cytochrome P-450 1A2. [5]
4. Question: In which pair of conditions does the theophylline label describe clearance as decreased by 50% or more?
 1. Congestive heart failure and hepatic insufficiency
 2. Hyperthyroidism and cystic fibrosis
 3. Renal impairment in adults and hypertension

4. Iron deficiency anaemia and obesity

4. Explanation: The label states that clearance is decreased by 50% or more both in patients with congestive heart failure and in patients with hepatic insufficiency such as cirrhosis, acute hepatitis or cholestasis. Hyperthyroidism and cystic fibrosis are listed among the factors that increase clearance. [1]

5. Question: Which methylxanthine is licensed for the short-term treatment of apnoea of prematurity?

1. Caffeine citrate

2. Aminophylline

3. Pentoxifylline

4. Theophylline extended-release tablets

5. Explanation: Caffeine citrate injection and oral solution are indicated for the short term treatment of apnoea of prematurity in infants between 28 and under 33 weeks gestational age. [3]

6. Question: Which electrolyte abnormality was recorded in the large majority of acute theophylline overdose cases in the series tabulated in the label?

1. Hypokalaemia

2. Hypernatraemia

3. Hypocalcaemia

4. Hyperkalaemia

6. Explanation: Low potassium appears in 85% and 79% of acute overdose cases across the two series in the label's table of manifestations of theophylline toxicity, and in 44% and 43% of chronic overdosage cases. [1]

Frequently asked questions

1. Question: Why does theophylline need blood level measurement when most bronchodilators do not?

1. Answer: Because the useful and the dangerous concentrations sit close together and clearance is unpredictable.

The label reports bronchodilation from 5 to 20 mcg/mL, rising adverse reactions above 20 mcg/mL, and a fourfold variation between otherwise similar adults in the amount needed to reach the same concentration. It adds that no single dose provides both safe and effective concentrations across a population, which is exactly why the concentration itself has to be measured. [1]

2. Question: What is the difference between theophylline and aminophylline?

2. Answer: Aminophylline is a 2:1 complex of theophylline with ethylenediamine, approximately 79% anhydrous theophylline by weight, and it is the form given by slow intravenous injection or infusion. The active moiety is the same, so the monitoring and interaction problems carry over, but the ethylenediamine component adds a hypersensitivity risk of its own, including exfoliative dermatitis in previously sensitised patients. [2]

3. Question: Why are these drugs used so much less than they once were?

3. Answer: Because the alternatives are better and safer for the same job. The aminophylline label names inhaled beta-2 selective agonists and systemically administered corticosteroids as the treatments of first choice in acute asthma exacerbations, and reports that most emergency department studies found adding intravenous theophylline produced no greater bronchodilation while increasing adverse effects. The oral label similarly discourages raising the dose during an exacerbation on the grounds that it adds little to inhaled therapy. [2][1]

4. Question: Which changes in a patient should prompt a fresh theophylline concentration?

4. Answer: A new illness or worsening of a chronic one, a sustained fever, starting or stopping smoking, and any addition or withdrawal of a medicine known to alter clearance. Heart failure and liver disease both cut clearance by half or more, and the label warns that stopping a drug which had been increasing clearance leads to accumulation to potentially toxic levels unless this is anticipated. [1]

5. Question: Are caffeine-containing drinks a problem during treatment?

5. Answer: MedlinePlus advises avoiding large amounts of coffee, tea, cocoa and chocolate during treatment, because they may increase the side effects caused by theophylline. Dietary caffeine is listed in the label among substances not producing a clinically significant pharmacokinetic interaction, so the concern is additive stimulant effect rather than a

change in the theophylline concentration. [7][1]

References

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