XANTHINE DERIVATIVES

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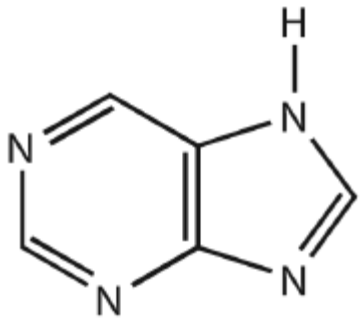
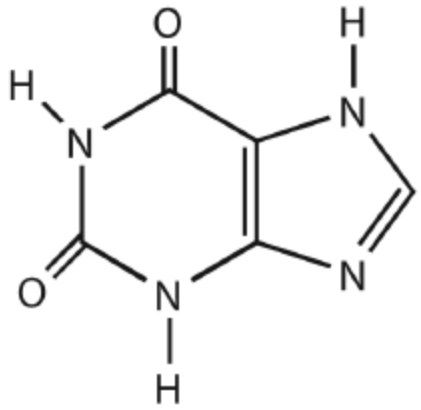
Source and Medicinal Chemistry

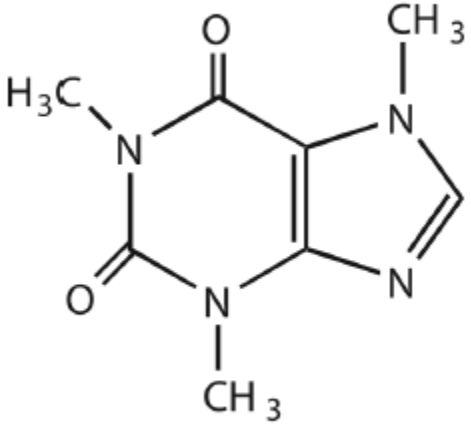
- Caffeine and theophylline
- The compounds contain the purine nucleus and are naturally occurring xanthine derivatives.
- Caffeine is the most active component of coffee, and coffee beans (seeds) of *Coffea arabica*, a small evergreen shrub abundant in the tropical areas of South America, Central America and the Middle East.
- It is also found in *Cola accuminata* and *Cola nitida*, tropical nuts of South America and Africa.



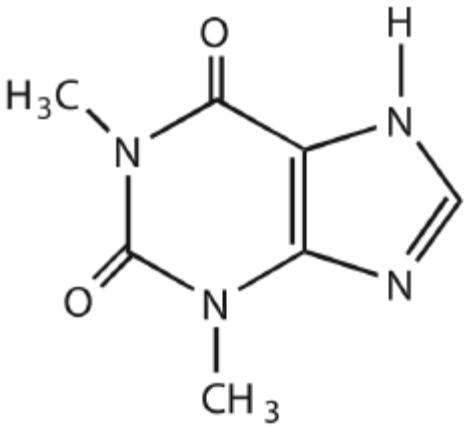
Purine



Xanthine



Caffeine



Theophylline

Structure of purine and xanthine derivatives

Caffeine and Theophylline Major Properties and Actions

Chemical	Botanical source	Predominant pharmacological actions	Therapeutic uses
Caffeine	*Coffea arabica* (coffee beans, seeds of the small evergreen shrub) *Cola accuminata* and *Cola nitida* (tropical nuts) *Thea sinensis* (leaves of the tea shrub) *Theobroma cacao* (seeds of the cocoa plant)	CNS stimulant Cardiac & skeletal muscle stimulant Smooth muscle relaxation Coronary vasodilator Increases BMR	Migraine headaches; weight loss; Wakefulness Improve mental alertness Relieve drug-induced respiratory depression; For short-term treatment of apnea in premature infants; Emergency cardiac stimulant Diuretic
Theophylline	*Thea sinensis* (leaves of the tea shrub)	Bronchodilator, pulmonary smooth muscle relaxation Increases BMR	Treatment of bronchial asthma and other respiratory-related disorders

Occurrence

- Caffeine is distributed throughout coffee, tea, chocolate, and cola beverages.
- Coffee beans and tea leaves containing equivalent amounts of the stimulant (up to 2%).
- Brewed coffee contains the highest amounts of caffeine (up to 100 mg), instant and decaffeinated coffees contain less (up to 75 mg and 5 mg, respectively), while a cola beverage possesses a significant dose of stimulant (up to 55 mg).

Pharmacology and Clinical Use

- Caffeine exert its pharmacological actions by increasing calcium permeability in sarcoplasmic reticulum. Inhibiting phosphodiesterase, promoting accumulation of cyclic adenosine monophosphate (cAMP). Act as a competitive, nonselective antagonists of adenosine A_1 and A_{2A} receptors.

- Theophylline, in addition, inhibits action of extracellular adenosine (bronchodilation). Stimulates endogenous catecholamines (central stimulant effect). Directly promotes mobilization of intracellular calcium and β-adrenergic agonist activity (airway smooth muscle relaxation).

- Caffeine stimulates cerebral activity, skeletal and cardiac muscle contraction, and general basal metabolic rate, while theophylline has less central stimulation but significant bronchial smooth muscle relaxation properties.

- Caffeine is available in combination with ergotamine, belladonna alkaloids or pentobarbital for the treatment of migraine headaches, for its synergistic action with ephedrine for weight loss and as an aid for wakefulness and restoring mental alertness.

- In combination with sodium benzoate (injectable), caffeine is used in the treatment of drug-induced respiratory depression, and as caffeine citrate (injectable) for the short-term treatment of apnea in premature infants.

- Theophylline is employed in the treatment of bronchial asthma and other respiratory-related disorders.

- Caffeine and theophylline enhance cardiac muscle contraction, induce coronary vasodilation and promote diuresis.

Toxicokinetics

- Xanthine derivatives are well absorbed orally, reaching peak distribution within two hours.
- The compounds are metabolized by the liver to methylxanthine and methyluric acid derivatives.
- Metabolic variability among different age groups, smokers and individuals with pathologic complications is probably due to variable levels of cytochrome P450 and N-acetyltransferase systems.
- The drugs are eliminated by the kidney with a half-life of 3 to 15 hours in nonsmokers (4-5 hr in adult smokers).

Signs and Symptoms and Clinical Management of Caffeine Toxicity

- The estimated lethal dose of caffeine in humans is 5 to 10 g.
- Although fatalities are unlikely approaching this dose, individuals who ingest up to 10 mg/kg are at risk of developing dysrhythmias or strychnine-like seizures.
- More likely adverse effects of excessive caffeine intake are demonstrable as CNS stimulation, including insomnia, restlessness, sensory disturbances and delirium.

- Increased skeletal muscle tension, tachycardia, premature ventricular contractions, diarrhea, development of peptic ulcers, and GI bleeding complete the detrimental properties of acute and chronic ingestion.

- Myocardial tachyarrhythmias and development of seizures should be monitored in patients after an acute ingestion of 1 g or more of caffeine.

- A short acting β-adrenergic blocker, such as esmolol, is useful in the management of the former.

- Seizures are controlled by a short acting benzodiazepine, such as midazolam.

Signs and Symptoms and Clinical Management of Theophylline Toxicity

- Theophylline shares similar properties with caffeine, although its toxicity is more acute and more common. Chronic toxicity, however, is unlikely.

- Therapeutic blood levels are strictly regulated at 10 to 20 µg/mL.

- Seizures occur between 25 to 40 µg/mL.

- Rapid IV administration of theophylline is associated with headache, hypotension, dizziness, restlessness, agitation and arrhythmias.

Tolerance and Withdrawal

- Caffeine withdrawal is associated with chronic use, and is demonstrated abruptly within 12 to 24 hours after the last dose.

- Initial symptoms include headache, anxiety, fatigue and craving behavior, last for about one week.

- There is demonstrated tolerance to the diuretic action and the insomnia produced with theophylline, but no tolerance develops to the CNS stimulation or bronchodilation.

Cardiovascular Drugs

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DIGITALIS GLYCOSIDES

Digitalis glycosides (DGs) have played a prominent role in the therapy of congestive heart failure.

Digoxin in particular remains widely used today despite increasing rates in heart failure and atrial fibrillation and the emergence of newer medications.

Medicinal Chemistry

DGs is a steroid nucleus containing an unsaturated lactone at the C17 position and three glycoside residues at the C3 position.

Digoxin differs from digitoxin only by the presence of a hydroxyl group at C12, which makes digitoxin more lipophilic than digoxin.

Although digitoxin is still available, digoxin is the most widely prescribed drug of this class in the United States.

This is principally because the techniques for measuring serum levels are readily available, it possesses flexible routes of administration, it has an intermediate duration of action, and it has a long history of therapeutic use.

Pharmacology and Clinical Use

DGs have been widely used for more than two centuries as therapeutic agents for congestive heart failure.

The drugs have a positive inotropic effect on failing myocardium and consequently increase the ability to control ventricular rate in response to atrial fibrillation.

DGs at therapeutic doses selectively bind and partially inhibit the intrinsic membrane protein $Na^+ – K^+$ -ATPase.

This partial inhibition of the Na^+ – K^+ -ATPase leads to an increase in the intracellular Na^+ concentration.

This will lead to reduce Ca^{2+} extrusion via the Na^+/Ca^{2+} exchange system in the sarcolemma.

The resulting increase in cytosolic and sarcoplasmic Ca^{2+} concentrations enhances the force of cardiac muscle contraction.

It was recently recognized that DGs are also able to modulate sympathetic nerve system activity, an additional mechanism contributing to their efficacy in the treatment of patients with heart failure.

Toxicokinetics

Absorption of DGs occurs in the gastrointestinal tract.

Because digoxin has greater polarity than digitoxin, GI absorption of digoxin is less rapid and less complete than the latter.

DGs bind to plasma proteins, especially albumin.

Highly protein-bound substances displace DGs from circulating albumin and increase the levels of free DGs in blood, thus potentially increasing their toxicity.

Once absorbed into the systemic circulation, DGs are widely distributed throughout the body, with the highest concentrations in muscular tissues.

Concentrations of DGs in the myocardium are about 30 times higher than those in blood.

DGs are mainly metabolized in the liver and in the GI tract.

Routes of elimination include urine and bile.

The half-life of digoxin is about 36 hours, whereas that of digitoxin is five to seven days.

Digitoxin’s high lipid solubility and recirculation through the enterohepatic pathway is partially responsible for its long half-life.

Because the liver and kidneys are significantly involved in the metabolism and excretion of DGs, the half-life of DGs may be significantly prolonged, with an increased likelihood of intoxication in patients with impaired renal and hepatic function.

These features contribute to its narrow therapeutic index (∽1.2–1.7 ng/mL), thus creating a slight partition between effective therapeutic concentrations and toxic manifestations.

Clinical Manifestations of Toxicity

Because signs and symptoms of digoxin toxicity are mostly nonspecific, a high index of suspicion is crucial for early recognition and appropriate management.

Acute poisoning occurs in adults following an intentional ingestion of a large dose or unintentional ingestion in children.

Chronic poisoning is more common in the elderly or heart failure patients receiving DGs and usually results from either inadvertent medication error or faulty patient compliance.

The incidence and severity of DG toxicity have been substantially reduced in the past two decades due partially to the development of alternative drugs for the treatment of heart failure as well as to the improved management of DG intoxication.

Manifestations of DG toxicity involve the CV, the CNS, and the GI tract.

The hallmark of cardiac toxicity is an increased automaticity coupled with concomitant conduction delay.

Premature ventricular beats, bradyarrhythmia, paroxysmal atrial tachycardia with block, junctional tachycardia, and bidirectional ventricular tachycardia are common.

DG toxicity is also manifest as dysfunction of CNS, including delirium, fatigue, malaise, confusion, dizziness, abnormal dreams, blurred or yellow vision, and halos.

Disturbances of color vision are frequently reported, a patient's complaint of a "whitish, yellowish halo vision" is a suspicious sign of digoxin intoxication.

GI disturbances may include anorexia, nausea, vomiting and abdominal pain.

Mechanisms of Toxicity

The toxic effects of DGs are, at least partially, the extensions of their pharmacological actions.

At therapeutic, nontoxic doses, digoxin increases vagal tone and decreases sympathetic activity, resulting in decreased SA and AV node automaticity.

At higher concentrations, toxicity progresses to induction of bradycardia, prolongation of AV conduction, or heart block.

It is also noteworthy that toxic doses of digoxin can increase both intracellular Ca^{2+} loading and sympathetic nerve system activation, precipitating atrial and ventricular dysrhythmias, including the life threatening ventricular fibrillation.

DGs may cause vasoconstriction as a result of increased intracellular Ca^{2+} in smooth muscle of the vessel wall.

CNS toxicity of DGs appears to be related to the inactivation of Na^{+} –K^{+} - ATPase, resulting in altered ionic transport across excitable neuronal membranes with consequent membrane irritability and instability.

Clinical Management of Intoxication

Successful management of DG intoxication depends on early recognition.

Treatment depends on the clinical conditions rather than serum drug levels.

Management varies from temporary withdrawal of the medication, general supportive care and proper treatment of the DG-induced cardiac arrhythmias to administration of digoxin-specific Fab fragments (i.e., Digibind) for life threatening CV compromise.

Digoxin-specific Fab fragments are antigen-binding fragments of antidigoxin antibody derived from immunized sheep.

Its high volume of distribution, which promotes entry into extracellular spaces, coupled with an elevated half-life (15–20 hours), and the antibody's significantly higher competitive affinity for digoxin, fashions a molecule that competitively binds and removes circulating and receptor-bound digoxin.

The antitoxin is indicated when serum digoxin concentrations are greater than 10 ng/mL (about 10 mg oral dose in adults, 4 mg in children) and serum potassium concentrations reach 5 meq/L or higher.

The usual dose of Digibind is calculated according to the number of digoxin tablets ingested.

Adults receive 20 vials (10 vials for children) of 40 mg/vial intravenously, and the dose is repeated as needed until signs and symptoms or serum digoxin levels fall.

Chronic intoxication requires about six vials of Digibind and administered as above.

The effect is demonstrated within minutes. Each vial (40 mg) binds 0.6 mg of digoxin; thus the number of Digibind vials (N) required for neutralization of DG toxicity is calculated on the basis of the total amount of digoxin, or number of digoxin tablets ingested (times 80% for incomplete absorption).

The number of vials required can also be calculated from the known SDC:

$$N = \frac{\text{SDC(ng/mL)} \times \text{patient weight (kg)}}{100}$$

Since Digibind is a biological product of immune origin, its major adverse drug reactions are consistent with therapeutic agents of that class, predominantly manifested as erythema, rash and urticaria.

Methods of Detection

Detection of the serum levels of DGs is of critical importance for the diagnosis of DG intoxication.

Drug-specific radioimmunoassays are the most widely used methods for detecting DGs in serum, with relatively new immunoassays currently available (Digoxin III, Abbott Laboratories, Illinois, U.S.).

Enzyme, chemiluminescence, and fluorescence polarization immunoassays are also available.