XANTHINE DERIVATIVES

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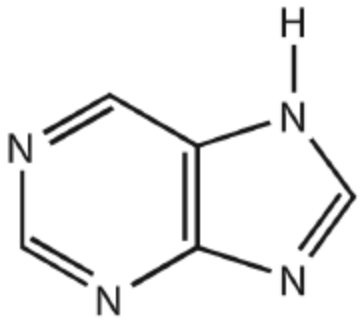
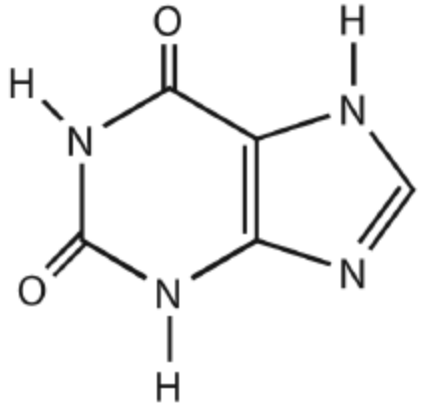
Source and Medicinal Chemistry

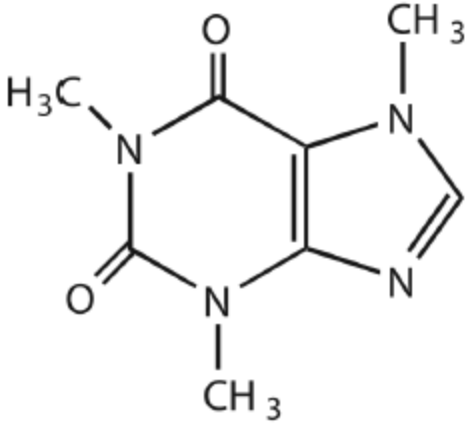
- Caffeine and theophylline
- The compounds **contain** the **purine nucleus** and are **naturally** occurring xanthine **derivatives**.
- **Caffeine** is the most **active component** of coffee, and coffee beans (seeds) of *Coffea arabica*, a small evergreen shrub abundant in the tropical areas of South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



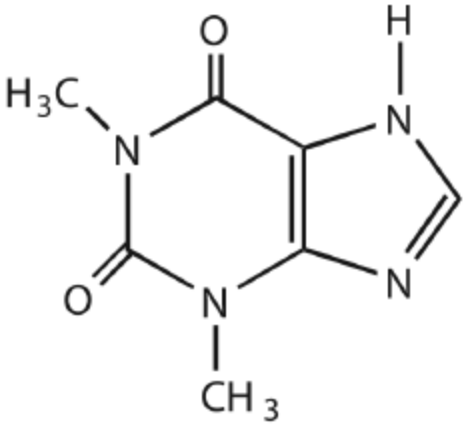
Purine



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

Dr. Ahmed Faisal

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.


THE END