Caffeine

CAS number: 58-08-2
MF: $C_8H_{10}N_4O_2$
FW: 194.2
Solubility in water 2.2%; soluble in ethyl acetate and chloroform; moderate soluble in alcohol and acetone; slightly soluble in ether and benzene.

Major uses
Caffeine (1,3,7-trimethylxanthine) found mainly in pharmaceuticals, food additives and a variety of common beverages (e.g. coffee, tea, cola drinks and other soft drinks) [1, 2].

Caffeine was first isolated from coffee in 1820. Beans from coffee Arabica, grown mostly in Central and South America, contain about 1.1% caffeine. Tea leaves contain about 3.5% caffeine [3].

Caffeine is a broadly used drug (often in a combination with other compounds) as the central nervous system (CNS) stimulant and a mild antidepressant. It is also widely used in headache preparations and pain relievers.

Human toxicity
In an adult person, acute ingestion of 1 g of caffeine causes reactions mainly referred to the CNS and circulatory system. Among CNS disorders, confusion, tremors, headache, convulsions, and even delirium have been described. Cardiac symptoms may include tachycardia, hypotention, dysrhythmias and cardiac arrest (asystole). Fever, vomiting and diarrhea can also take place [1, 4].

Estimated minimum lethal dose is in excess of 5 g (the equivalent of 40 strong cups of coffee taken in a very short space of time). In adult man, the minimal lethal dose distributed intravenously is 57 mg/kg and orally 150 to 210 mg/kg body weight [1, 5], whereas the minimal oral lethal dose in women is reported to 400-1000 mg/kg [5]. Mean lethal dose of caffeine was estimated to be 10 g [6].

Therapeutic blood level is approximately 5 mg/l [7]. Mean lethal serum concentration, based on the data from several handbooks, is 120 mg/l [6].

Kinetic data
Absorption: Caffeine is absorbed 30 to 60 min after oral ingestion. Absorption after intramuscular administration is slower. Caffeine has a higher toxicity when it is administered intravenously than when it is given orally [1]. Toxic effects are reached in 3 h after an acute toxic dose [1].

Volume of distribution: 0.61 l/kg [1]. The distribution is equally rapid throughout the entire water pool of the body [1, 4].

Peak plasma concentration occurs 30 min to 2 h following caffeine ingestion.

Plasma half-life is about 3 to 4 hours in adults, but it is prolonged 2 to 3 times in the 3rd trimester of pregnancy [1, 4].

Plasma protein binding: approximately 17% [4].

Passage of blood-brain barrier is free. Caffeine also readily passes placenta.

Metabolism and excretion

Caffeine is a methylxanthine compound, chemically similar to theophylline and mainly metabolized in the liver by the microsomal enzymes, where it undergoes N-demethylation and phase II conjugation [1].

The metabolites of caffeine are [1]:

- Paraxanthine (up to 70% of the dose)
- 1-Methyluric acid (21 to 28%)
- 1-Methylxanthine (10 to 19%).
- 1,3-Dimethyluric acid (3 to 9%)
- 1,7-Dimethyluric acid (7%)
- 7-Methylxanthine (4 to 7%)
- 7-Methyluric acid (5%)
- 1,3,7-Trimethyluric acid (2.5%)
- 3-Methylxanthine (2%)
- Theobromine (1%)
- Theophylline (0.8%)

Caffeine and its metabolites are excreted in the bile, urine, and a trace in the feces [4]. 10% of a given dose of caffeine is excreted unchanged in the urine. Main metabolites excreted in the urine are 1-methyluric acid, 1-methylxanthine and acetylated uracil derivative [1, 5].

Toxicological mechanisms

Caffeine stimulates the CNS, acts on the kidney to produce diuresis, stimulates contractility of cardiac and skeletal muscle directly, and also inhibits the contractility of smooth muscle [1].

Caffeine competitively antagonizes cellular adenosine receptors, inhibits phosphodiesterase, stimulates catecholamine release, and increases free calcium and intracellular cAMP [5]. An overdose of caffeine results in surges of circulating catecholamines and renin. Norepinephrine, dopamine, and serotonin levels in the brain are also increased [1].

Target organs: CNS, heart, kidney [5].

References

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