

Codeine

CAS: 76-57-3

MF: C₁₈H₂₁NO₃

MW: 299.4 (anhydrous)

Solubility: very well soluble in water (1 g in 0.7 ml of water, 21°C).

Major uses

Codeine is the natural alkaloid and constituent of opium, together with morphine, papaverine and thebaine, all belonging to the class of opiates. Opium occurs in the poppy plant (*Papaver somniferum*). Codein has been first isolated from opium in 1832, by the French chemist P.-J. Robiquet. It is mainly used as a narcotic analgesic and a pain reliever, but also as an antitussive and an antidiarrheal drug. Moreover, codeine is used in numerous preparations in combination with no narcotic analgesics, antihistamines, and other drugs [1, 2].

Codeine is usually synthetically produced by 3-*O*-methylation of morphine. The drug is available as the phosphate (the most common salt of codeine) or sulfate salt.

Addiction to codeine can occur, however, the dependence is much weaker compared to morphine or heroine (diacetylmorphine) [1, 2].

Human toxicity

Codeine can be very poisonous and sometimes fatal at the large doses. Like morphine and the other opiates, the acute toxic effects of codeine include miosis (smaller pupil size), constipation, urinary retention, nausea and vomiting, hypothermia, drowsiness, dizziness, apathy, confusion, respiratory depression, hypotension, pulmonary edema, coma, and death at severe poisoning [1].

The total therapeutic daily dose may range from 60 to 240 mg [2].

The acutely lethal dose of codeine for an adult has been estimated at 0.5-1.0 g. The lowest reported lethal dose was reported to be 12 mg/kg. The lowest reported lethal dose was reported to be 12 mg/kg. Doses of this magnitude may cause unconsciousness and convulsions; and death from respiratory failure may result in 2-4 hours post-ingestion [1].

Therapeutic plasma levels may range from 0.03 to 0.34 mg/l in several studies (reviewed in [1]).

In the poisoning cases, blood codeine concentrations exceed 1.0 mg/l. Toxic plasma levels varied from 1.0 to 8.8 mg/l (average 2.8) in 11 poisoning cases [1, 2]. In one study, post-mortem blood codeine concentrations in 8 persons succumbing to codeine overdosage ranged from 1.4 to 5.6 mg/l (reviewed in [2]).

Kinetic data

Absorption: codeine is well absorbed following oral and parenteral administration [2].

Bioavailability: 50.2 ± 2.1% [3].

Volume of distribution: 3.5 l/kg [2].

Distribution: codeine is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by the liver, spleen, and kidneys [2].
Plasma half-life: 2.5-3.0 h [1].

Time to peak blood concentration: effects of codeine start at 10-30 min after ingestion, peak within 1 to 2 h, and may last 4-6 h, depending on dose [1].

Plasma protein binding: 7-25% [2].

Passage of blood-brain barrier: possibly free? (Data are not available). Codeine is converted to morphine in the brain, but only about 10% of ingested dose [1].

Elimination half-life: 1.9 to 4 h [1, 2].

Metabolism and excretion

Codeine is biotransformed in the liver via *O*-demethylation to morphine and via *N*-demethylation to norcodeine [2]. In most humans, about 10% of codeine is transformed to morphine. The enzyme responsible for the *O*-demethylation to morphine has been identified as cytochrome P450 (CYP2D6). This enzyme is missing in about 7% of the white population; therefore codeine not always is effective [4].

Codeine and its metabolites are excreted in the urine as both free drugs and as glucuronide conjugates [2].

Excretion: the elimination of codeine is primarily via the kidney, and about 90% of an oral dose is excreted within 24 h. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). Negligible amounts are excreted in the feces [2, 4].

Mechanisms of action

Codeine is an opiate agonist. It can, in similarity with morphine and some other opiates, activate opiate receptors in human brain, e.g. *mu* and *delta* receptors. *Mu* receptors are most highly concentrated in areas of the brain involved in pain sensation. These receptors have a high affinity for the morphine-like agonist drugs and produce analgesia, respiratory depression, miosis and euphoria when stimulated with these drugs [5]. The role of the *delta* receptor has not been fully understood. The stimulatory effects of opioids are the result of "disinhibition" as the release of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) and acetylcholine is blocked. The exact mechanism how opioid agonists can cause stimulatory effects is not well understood [4].

Toxicological mechanisms

The mechanisms of toxicity are not well understood.

Opiates produce major toxic effects on the central nervous system (CNS) and the cardiovascular system. They depress the rate but not the depth of respiration by decreasing the sensitivity of the medullar respiratory centers* in the brain to the level of arterial carbon dioxide. Hypoxia (the lack of oxygen in tissue) develops and is a cause of death in almost all fatal opiate intoxications [5].

Target organs: CNS, heart/cardiovascular system, kidney, liver [5].

References

1. Poisindex, Thomson Micromedex (2006).
2. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th ed., pp. 191-194. Chemical Toxicology Institute, Foster City, CA, USA.
3. Hull, J.H., Findlay, J.W., Rogers, J.F., Welch, R.M., Butz, R.F., Bustrack, J.A. (1982) An evaluation of the effects of smoking on codeine pharmacokinetics and bioavailability in normal human volunteers. *Drug Intell Clin Pharm* 16(11), 849-854.
4. Codeine information. Via internet: <http://www.findrxonline.com/codeine.htm>
5. Haddad, L.M. & Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 706-717. W.B. Saunders Company.

* The *medulla oblongata* is the lower portion of the brainstem, where the centers for the control of autonomic functions (such as breathing and heartbeat) are located.

Written by Ada Kolman, February 2006; revised March 2007
Ada.kolman@telia.com