

Chloral hydrate

Synonym: trichloroacetaldehyde hydrate

Chemical name: 2,2,2-trichloroethane-1,1-diol

CAS: 302-17-0

MF: $\text{Cl}_3\text{CCH}(\text{OH})_2$

MW: 165.4

log Kow=0.99

pKa=6.8

Solubility: soluble in water, acetone, benzene, chloroform, diethyl ether, ethanol, and methyl ethyl ketone [1].

Trichloroethanol (an active metabolite of chloral hydrate)

MF: $\text{Cl}_3\text{CCH}_2\text{OH}$

MW: 149.4

Solubility: soluble in 12 parts water; miscible with ethanol or ether [2].

Major uses

Chloral hydrate (synthesized in 1832 and introduced into medicine 1869) is the oldest member of sedative-hypnotic drugs. To the same group belong paraldehyde, bromide, urethane, and sulfonal. Metabolite of chloral hydrate, trichloroethanol, is also an excellent hypnotic agent, but is not often used as such due to its physical and irritant properties. At present, chloral hydrate is largely displaced by using of benzodiazepines and barbiturates [3].

Chloral hydrate is used as a chemical reagent and precursor. The anhydrous form is an intermediate in the synthesis of the insecticides (DDT, methoxychlor, naled, trichlorfon, and dichlorvos), and the herbicide trichloroacetic acid [1].

Chloral hydrate is also used as an anesthetic agent in the veterinary medicine [1].

Human toxicity

The usual adult hypnotic dose is 0.5 to 2 g; and, as a sedative, 0.25 g 3 times a day (equivalent to 10.7 mg/kg body weight per day) up to a maximum single or daily dose of 2 g [6, 7]. Such adverse effects as the central nervous system (CNS) depression, vomiting and gastrointestinal tract irritation can occur at therapeutic doses.

Significant overdose may result in ventricular dysrhythmias, cardiac arrest, respiratory depression, hypotension, and coma. Response to overdose amounts of chloral hydrate can be quite variable. Individuals with known cardiac dysfunction are highly susceptible to toxicity.

Toxicity generally develops within 2 to 3 h of ingestion. Lethal symptoms are the CNS depression and respiratory arrest, but above all heart arrhythmias. Death occurs in a few hours [4, 5].

Since chloral hydrate is undetectable in plasma, determination of plasma trichloroethanol concentrations can be useful in estimating of amount of drug ingested and the severity of overdose. Trichloroethanol is thought to be responsible for the effect of chloral hydrate [6].

The lethal oral dose in humans averages about 10 g, but varies greatly. Fatalities have followed the ingestion of 1.25 and 3 g, but recovery has occurred after the ingestion of 30 g [7].

The therapeutic range of plasma/serum blood concentration of trichloroethanol in adults is between 10 and 20 mg/l when 1 g of chloral hydrate was taken orally [5]. At

overdose, the blood concentrations can be dramatically increased. Post-mortem levels of trichloroethanol in blood plasma ranged from 55 to 550 mg/l [8].

Carcinogenicity: there are no carcinogenicity data from humans [6].

Kinetic data

Absorption: chloral hydrate is rapidly absorbed in the gastrointestinal tract and starts to act within 30 min (it is metabolically converted in trichloroethanol, see Metabolism).

Kinetics: possibly linear kinetics for trichloroethanol.

Distribution: chloral hydrate is rapidly distributed to all organs, including brain. Both chloral hydrate and trichloroethanol are highly lipid soluble and permeate plasma membranes to enter cells throughout the body [3].

Accumulation in vital organs: some amount of chloral hydrate is accumulated in liver.

Volume of distribution (V_d): for chloral hydrate $V_d=0.75$ l/kg; for trichloroethanol $V_d=0.6$ l/kg. In one case of intentional poisoning (ingestion of 38 g of chloral hydrate) V_d for trichloroethanol was reported to be 1.6 l/kg [9].

Passage of blood-brain barrier: free.

Plasma half-life for chloral hydrate is only 4 to 5 minutes [3]. Therapeutic half-life for trichloroethanol is 6 to 12 h; at overdose – up to 35 h [5]. Plasma half-life for another metabolite, trichloroacetic acid, is more than 30 h [3].

Time to peak blood concentration for trichloroethanol: 1 h.

Plasma protein binding: 35 to 41% for trichloroethanol; and 71 to 88% for trichloroacetic acid [3].

Elimination: mainly renal, after conjugation with glucuronic acid. Small amount is eliminated via gall-bladder.

Metabolism and excretion

Chloral hydrate is rapidly metabolized (half-life of 4 minutes) to trichloroethanol by enzyme alcohol dehydrogenase (by using nicotinamide adenine dinucleotide, NAD, as a cofactor) in both hepatic and extrahepatic tissues. A small but variable amount of chloral hydrate and trichloroethanol are further oxidized, mainly in the smooth endoplasmic reticulum of the liver and kidney, to inactive trichloroacetic acid with a help of an aldehyde dehydrogenase, which is located in both liver and erythrocytes. A portion of the trichloroethanol produced is conjugated with glucuronic acid. The majority of the trichloroethanol glucuronide is excreted in the urine. A minor metabolite of chloral hydrate is also dichloroacetic acid [3].

In a daily life, the major route of human exposure to chloral hydrate is from drinking-water (approximately 5 $\mu\text{g/l}$ or less). Chloral hydrate and its metabolites, trichloroacetic acid and dichloroacetic acid, are formed as by-products when water is disinfected with chlorine [4].

Excretion: between 16 and 35% of the chloral hydrate dose is excreted in the urine in 24 h as trichloroethanol and its glucuronide. About 5% is excreted as free trichloroethanol. A small amount of trichloroethanol glucuronide is excreted into the bile [4, 5].

Toxicological mechanisms

The knowledge is insufficient. Chloral hydrate is biotransformed in the liver to the active metabolite trichloroethanol, which is responsible for the toxicity of this drug at overdose. Cardiac arrhythmias and cardiovascular collapse are most typical features of acute intoxication. However, the mechanisms of a direct cardiac toxicity of this drug are still unknown.

A CNS depression, manifested as deep stupor and coma, as well as a skin and mucous membrane corrosive effects are also typical features of toxicity [3].

Trichloroethanol and trichloroacetic acid produce free radicals and induce lipid peroxidation when studied in *in vitro* system using microsomes from mice (reviewed in [1]).

Target organs: heart, CNS, liver [3].

References

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