Review Article

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Chloral Hydrate Poisoning with Analytical aspects and its Management

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Abstract

Chloral hydrate has been used by criminals, doctors and in various other industries. The interest in this drug has been rekindled since it is now popularly being used as Date rape drug. Also recent studies have shown increased health risks with commercial use of chloral hydrate. This paper has been written with the aim of highlighting the analytical aspects and management of Chloral hydrate poisoning.

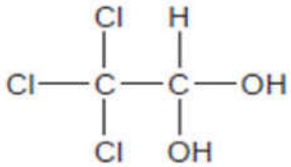
Keywords: Chloral Hydrate; Poisoning; Analysis; Management.

Introduction

Chloral hydrate (a.k.a. Dry wine, Noctec, Knockout drops; Mickey finn, Choral, Hydrated choral, Chloralex, Chloralvan, Novochlorhydrate, Chloraldural, Chloraldurat, Trichloralacetaldehyde hydrated, Trichloroethylidene glycol, 2,2,2-Trichlorethane-1,1-diol) is a colorless, crystalline substance with a pungent pear like odor and bitter taste. It was first synthesized in 1832 by Justus von Liebig [1] and first used as a sedative and hypnotic in 1869. It is often used as a recreational drug. Its structure is similar to that of ethyl alcohol. It is also a drug of abuse.

Chemical Formula: CCl3CH2

Chemical Structure



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Sources [2-5]

1. Formulations marketed include gargles, lotions or solutions used as mouth bath (owing to CH analgesic and disinfectant properties).
2. Syrups prescribed as sedatives in elderly .
3. Available as rectal suppositories.
4. Short term sedation in children during non painful procedures (CT scan).
5. Treatment of alcoholism and strychnine poisoning.
6. Psychiatric hospital.
7. Mickey finn – a combination of chloral with alcohol or with croton oil.
8. Knock out drops.
9. Metal cleaning and degreasing operations.

Exposure

TCE has been detected in air, water, soil, food, and animal tissues. The most heavily exposed people are those working in the degreasing of metals, mainly through inhalation of vapor. In united states the maximum contaminant level of groundwater is 5 μg/L [6].

Pharmacokinetics

Mechanism of Action

Chloral hydrate is a central nervous system (CNS) depressant. It has also been classified as a Stupefying agent. The initial depressant effect is due to Chloral hydrate, but prolonged CNS depression is primarily

due to trichloroethanol. The detailed mechanism by which chloral hydrate and trichloroethanol depress CNS is not completely known.

Metabolism

Chloral hydrate is well absorbed from the gastrointestinal tract, producing pharmacological action within 30 min. It is rapidly metabolized to trichloroethanol by alcohol dehydrogenase, which is pharmacologically active. A small amount is metabolized to an inactive metabolite, trichloroacetic acid. Trichloroethanol is either conjugated with glucuronic acid to form urochloralic acid or oxidized by aldehyde dehydrogenase to trichloroacetic acid. It is excreted in urine as trichloroacetic acid and urochloralic acid.

Half Life: Chloral hydrate - few minutes, Trichloroethanol - 4 to 14 h.

Exposure Limit: According to US Environmental Protection Agency (EPA) regulations, up to 1999, the maximum contaminant level and the maximum contaminant level goal for trichloro acetaldehyde, was 60 and 40 mg/ l, respectively [7].

Fatal Dose: 5-10 g. Acute ingestion of 2 g is likely to lead to toxic symptoms

Fatal Period: 8–12 h.

Normal reference values - Therapeutic oral dose in adults >0.5-2gm.

Signs and Symptoms of Chloral Hydrate Poisoning (Table 1).

Table 1: Signs and symptoms of chloral hydrate poisoning

	Features
Acute poisoning	• GI tract: nausea, vomiting, retrosternal burning sensation, hemorrhagic gastritis, stomach or intestinal perforation, esophageal stricture formation. • General – Odor *(Acrid pears like)*, pupils – initially miotic and then dilate, hypothermia • Skin: Scartinal or urticarial rash • CNS – ataxia and lethargy, deep coma within couple of hours. • CVS – Atrial fibrillation, supraventricula tachycardia, ventricular arrhythmias, torsades de pointes, Ventricular fibrillation, asystole and hypotension. • Hepatorenal – renal and hepatic failure The combination of deep coma and dysrhythmias without hypoxia is typical of chloral hydrate poisoning.
Chronic poisoning	• Skin – erythematous and urticarial eruptions • GIT – irritation • CNS – Convulsions, tremors • Respiratory system – dyspnea • Liver damage • Delirium tremens, seizures, psychosis may be seen • Certain studies have shown increased incidence of carcinomas in mice. [4]

Biomarkers [8]

A biomarker can be broadly defined as any biological index capable of being measured that is associated with or indicative of a defined biological endpoint such as a developmental or disease stage. Typically, biomarkers are defined as quantitative measures of changes in the biological systems that respond to either (or both) exposure and/or doses of xenobiotic substances that lead to biological effects.

The malondialdehyde-modified DNA adduct, 3-(2-deoxy-$-D-erythro-pentofuranosyl) pyrimido[1,2"] purin- 10(3H)-one (MDA-MG-1), is formed from the metabolism of 1 mM chloral hydrate, trichloroacetic acid, and trichloroethanol by control B6C3F1 mouse liver microsomes, mouse pyrazole-induced microsomes, male F344/N rat liver microsomes, and human liver microsomes in the presence and absence of calf thymus DNA . MDA-MG-1 is persistent in the mouse liver, having a t½ of 12.5 days [9] therefore, it could serve as a biomarker for the study of xenobiotic-induced and naturally formed lipid peroxidation and endogenous DNA adduct formation [10]. Biomarkers for metabolites of TCE in animal models include a chloral-protein adduct which has been detected in tissues of TCE-treated mice [11].

One study revealed a time- and concentration-dependent release of LDH after normal human epidermal keratinocyte cells were exposed to different doses of TCE [8].

A significant decrease in total epididymal sperm count, sperm motility, specific activities of enzymes glucose 6-phospho dehydrogenase, and 17 α-hydroxy steroid dehydrogenase with a concomitant

decrease in serum testosterone concentrations in TCE-inhaled rats was recorded by Kumar et al[12]. High and long-term exposure of TCE to persons results in an increase in the level of á1-microglobulin excretion, which is a potential biomarker of renal toxicity[13]. The specific content of CYP3A in liver microsomes was found to be increased more than 2-fold by the administration of TCE [14].

No plant based biomarker for chloral hydrate or TCE has been found in literature.

Analytical Aspects and Management

A. *Colour Tests*[15]: Fujiwara test - 3 to 5 cc. of concentrated (17 to 25 per cent) NaOH solution in a test-tube are superimposed with a layer 2 mm. thick of pyridine. A small quantity of the substance or a drop of the solution to be tested is added and the contents of the tube are raised to the boiling point, shaking well to avoid bumping. If the color has not appeared when the mixture has boiled a few seconds, the test tube should be shaken vigorously and then held still until the pyridine layer has risen to the surface. If chloral hydrate is present the pyridine will be colored from a pink to a clear deep red [16,17].

B. *Spectrophotometric Tests:* Treat the substance with quinaldine ethyl iodide to form a blue cyanine dye. The quantity of the dye can be measured spectrophotometrically.

C. Gas chromatography (GC) can be used for quantitative analysis of chloral and its hydrate, which breaks down to chloral on vaporization[18].

D. Liquid–liquid extraction and GC with electron capture detection (GC–ECD), has a detection limit of 0.005 g/L [15,19,20]

E. An indirect differential pulse polarographic method for the determination of formaldehyde and chloralhydrate is described by Sulaiman et al, based on the oxidation of the alkaline sample solutions of formaldehyde and chloralhydrate with a chloroform solution of iodine and removal of its excess. The resulting iodide is oxidized with bromine water and measured polarographically as iodate (at pH 9.3) with sixfold amplification [21].

F. Bruzzoniti et al have studied two liquid chromatographic methods, based on reversed-phase (RP) and anion-exchange mechanisms, for chloral hydrate determination. They have determined that at equimolar concentration 1,2-benzenedithiol can be used for determination of relatively high chloral hydrate concentration by RP (.20 mg/ l) at wavelength of 220 nm. The method developed enables the determination of chloral hydrate at concentration levels (0.2 mg/ l) [7].

Interactions of Chloral Hydrate with Other Substances

Chloral with furosemide can cause undesired haemodynamic effects possibly due to the displacement of chloral hydrate metabolites from the protein-bound state by furosemide [22].

Chloral hydrate with ethanol may cause tachycardia and hypotension even in therapeutic dose possibly because Chloral hydrate slows down the reduction of ethanol by competition for ADH and ethanol enhances the conversion of chloral hydrate to TCE [23].

Management [2,4]

1. Gastric lavage (based on the patient's level of consciousness and history of ingestion) with alkaline solution.
2. Activated charcoal to adsorb chloral hydrate
3. Monitoring
4. Intubation if reduced gag reflex
5. Scandinavian measure
6. Treatment of cardiac arrhythmia:

a. Propranolol

b. Esmolol (short acting beta blocker)

c. Bretylium (adrenergic neuron blocking drug)

7. Treatment of hypotension

a. Infuse 10-20 ml/kg of isotonic fluid

8. Catecholamines (Class IA antiarrhythmics) are contraindicated as they precipitate ventricular arrhythmia
9. Flumazenil 200micro gram infusion followed by 100 microgram at 1 minute interval upto 3 times. Total dose 500 microgram.
10. There is no antidote for chloral hydrate poisoning.
11. Forced diuresis is not useful.
12. Hemodialysis and hemoperfusion useful in severe cases
13. Withdrawal reactions-managed with barbiturates or other sedative–hypnotic agents.

Postmortem Findings

Gastric mucosa is eroded, softened and reddened, and smells of chloral hydrate. Brain and lungs are congested. Damage to kidneys and liver may be seen.

Medico-Legal Aspects

Accidental poisoning results by taking large doses as a hypnotic. Suicidal/homicidal cases are rare. It is mixed with food or drink to render a person suddenly helpless for the purpose of robbery or rape (Date rape drug). Its action is so rapid, hence the name 'knockout drops'. Trichloroethylene has been included in the list of first 10 chemicals to be evaluated for risk under amended Toxic Substances Control Act by US environment protection agency in 2016. EPA is proposing to ban use of TCE in commercial vapor degreasing as a result of identified health risks [24].

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