**CHLORAL HYDRATE**  
*Sedative – Hypnotic*

**Pharmacology**: Chloral hydrate has general CNS depressant effects believed to be due to its active metabolite, trichloroethanol.

In doses used for hypnosis, chloral hydrate produces mild cerebral depression and quiet, deep sleep, usually with little or no hangover effects. Chloral hydrate decreases sleep latency and nighttime awakenings with minimal effects on REM sleep. REM rebound does not occur with drug withdrawal. Tolerance to the sedative effects may develop over a 5- to 14-day period of continued use.

At therapeutic doses, chloral hydrate has little effect on respiration and blood pressure. Higher doses may lead to depression of respiratory and vasomotor centres. Chloral hydrate has little analgesic activity and may produce excitement or delirium in the presence of pain. Sedative or hypnotic doses have little anticonvulsant activity.

**Pharmacokinetics**: Chloral hydrate is rapidly absorbed following oral or rectal administration. Following a hypnotic dose, drowsiness occurs within 10 to 15 minutes and sleep usually occurs within 30 to 60 minutes, which lasts about 4 to 8 hours. When used as a premedicant in children and infants, sedation usually occurs within 15 minutes and sleep by 40 minutes, with most fully awake within 2 hours.

Chloral hydrate is rapidly and extensively metabolized in the liver and erythrocytes by alcohol dehydrogenase to its major active metabolite, trichloroethanol. A small amount of chloral hydrate and a larger portion of trichloroethanol are oxidized to a minor, less active metabolite, trichloroacetic acid, in the liver and kidneys. This metabolite is excreted in the urine and bile, together with trichloroethanol in free or conjugated form.

The average half-life of trichloroethanol in adults is 8 hours, ranging from 4 to 12 hours. The half-life is prolonged in children (10 hours), preterm neonates (37 hours) and term neonates (28 hours). Trichloroethanol is 70 to 80% bound to plasma proteins and is widely distributed to all body tissues including CSF, breast milk and placenta.

The half-life of trichloroacetic acid is longer, up to 100 hours. It is highly plasma protein bound (94%), primarily to albumin and may be responsible for interactions with other highly protein bound drugs. Upon multiple dosing, trichloroacetic acid can displace bilirubin or warfarin from binding sites, potentially resulting in hyperbilirubinemia or hypoprothrombinemia.

**Indications**: For short-term use as a sedative or hypnotic. Tolerance to these effects often develops after a 2-week period. Chloral hydrate has also been used prior to surgery or other procedures to allay anxiety or to produce sedation or sleep, without depressing respiration or cough reflex. In postoperative care and control of pain, chloral hydrate may be used as an adjunct to opiates and analgesics. There is some evidence that chloral hydrate may alleviate the symptoms of alcohol or drug withdrawal.
**Warnings:** Abuse and Dependence: Chloral hydrate should be used as a hypnotic only for short-term use, usually 2 to 7 days. Prolonged use of chloral hydrate may produce tolerance and physical and/or psychological dependence. Sudden withdrawal after prolonged use may result in hallucinations and symptoms similar to delirium tremens (sometimes fatal), therefore chloral hydrate should be tapered gradually. Chloral hydrate should be used with caution in patients who are mentally depressed, suicidal or have a history of drug abuse or dependence.

**Cardiac Disorders:** In patients with severe cardiac disease, chloral hydrate should be avoided due to the possibility of cardiac arrhythmias and hypotension associated with larger doses.

**Gastrointestinal:** Because of its irritant properties, oral use of chloral hydrate should be avoided in patients with gastritis, esophagitis or gastric or duodenal ulcer. Rectal use should be avoided in patients with proctitis or colitis.

**Children:** Patients should be monitored for CNS and respiratory depressive effects. Deaths associated with the use of chloral hydrate for sedation prior to diagnostic or therapeutic procedures have been reported, particularly in pediatric patients. In addition, particular care must be taken in calculating and administering the proper dose.

Sedation with chloral hydrate in children with adenoidal hypertrophy and obstructive sleep apnea has been reported to cause episodes of life-threatening respiratory obstruction. Children with obstructive sleep apnea from other causes may be at risk as well. Laryngeal edema resulting in severe respiratory difficulty in a child has also been reported.

**Precautions:** Occupational Hazards: Due to chloral hydrate's sedative effects, patients should be warned against driving, operating dangerous machinery or engaging in other activities requiring mental alertness and physical coordination after taking the drug.

**Drug Interactions:** *Ethanol:* The combination of ethanol and chloral hydrate produces additive and possibly synergistic CNS depressant effects. A disulfiram-like reaction may occur, including tachycardia, facial flushing and dysphoria. Additive CNS effects may occur when chloral hydrate is given concurrently with other CNS depressants such as paraldehyde or barbiturates.

**Oral Anticoagulants:** Chloral hydrate may transiently enhance the hypoprothrombinemic response to warfarin, especially within the first 2 weeks of therapy, by displacing warfarin from plasma protein binding sites. When chloral hydrate is added or removed from the therapeutic regimen, or when dosage changes are made, frequent prothrombin time determinations are recommended.

**Drug-Laboratory Test Interactions:** Chloral hydrate may interfere with fluorometric determinations of urine catecholamines. Chloral hydrate should not be administered within 48 hours prior to the test. Chloral hydrate may cause elevations in urine 17-hydroxycorticosteroid. Administration of chloral hydrate can result in erroneously high values for vitamin B12 in some radioassay procedures.

**Pregnancy:** Chloral hydrate crosses the placenta. Safety has not been established. Chronic use during pregnancy may cause withdrawal symptoms in the neonate.
**Lactation:** Small amounts of chloral hydrate are excreted in breast milk. Use by nursing mothers may cause drowsiness in the infant.

**Children:** Gastric irritation and vomiting may occur following administration of the oral liquid. It should be well diluted with water or other liquid such as fruit juice or ginger ale.

Due to the prolonged half-lives of chloral hydrate's metabolites, excessive CNS depression may occur due to accumulation following repeated dosing. The degree of sedation should be monitored and caregivers cautioned against exceeding prescribed dosage.

Neonates should be monitored for increased bilirubin concentrations as hyperbilirubinemia may occur due to competition of chloral hydrate metabolites with bilirubin for hepatic glucuronidation.

**Geriatrics:** In elderly patients likely to have age-related hepatic/renal function impairment, and in debilitated patients or those patients prone to CNS depression, reduction of dose may be necessary to avoid oversedation or other adverse effects.

**Respiratory:** Careful monitoring is required in patients with respiratory insufficiency.

**Adverse Effects:** 

**Gastrointestinal:** The most frequent adverse effect of chloral hydrate is gastrointestinal irritation, manifested by nausea, vomiting, diarrhea and stomach pain. Unpleasant taste and flatulence may also occur. These effects can be minimized by taking chloral hydrate with a full glass of fluid. Ileus in an infant has been reported.

**CNS:** Adverse effects of chloral hydrate due to CNS depressant effects include: lightheadedness, ataxia, nightmares, drowsiness, vertigo, headache, confusion, and malaise. Most CNS effects occur infrequently. Hangover effect can occur, although it is less commonly observed than with barbiturates and some benzodiazepines. Rarely, paradoxical and idiosyncratic reactions (hallucinations, delirium, unusual excitement, disorientation, incoherence, paranoia) have occurred.

**Cardiovascular:** Large doses of chloral hydrate have been reported to produce hypotension, ventricular and atrial arrhythmias, torsades de pointes, depression of myocardial contractility, and shortening of refractory period.

**Respiratory:** Life-threatening respiratory obstruction episodes have been reported in young children (see Warnings).

**Dermatologic:** Dermatologic reactions are not common, but include: erythematous rash, urticaria, angioedema, eczematoid dermatitis, scarlatiniform exanthema, bullous lesions, non-thrombocytopenic purpura and erythema multiform. Some cutaneous reactions are accompanied by fever. Chloral hydrate is an irritant when applied to the skin and mucous membranes.

**Metabolic:** Chloral hydrate has been reported to precipitate attacks of acute intermittent porphyria. Rarely, ketonuria has been reported.

**Hematologic:** Leukopenia and eosinophilia have been reported.
**Ophthalmologic:** Chloral hydrate has produced oculotoxicities manifesting as ptosis, allergic conjunctivitis or keratoconjunctivitis.

**Other:** Increases in middle ear pressure in infants and children have been reported.

**Overdose:** Symptoms: Acute poisoning resembles barbiturate intoxication, producing symptoms of CNS depression and deep coma, respiratory depression, hypotension and cardiac arrhythmias. Death may result from respiratory or cardiovascular failure. Resistant cardiac arrhythmias account for most of the mortality. Individuals with known cardiac dysfunction are highly susceptible to toxicity.

Gastritis, nausea and vomiting are common. Gastric necrosis, perforation, gastrointestinal hemorrhage and esophageal stricture have also been reported. Other signs may include pinpoint pupils, cyanosis, hypothermia, muscle flaccidity and pulmonary edema. Renal damage (albuminuria) and hepatic damage (jaundice) may occur.

The usual lethal dose is 10 g; however, fatalities have occurred with as little as 4 g and survival has been documented after the ingestion of 30 g of chloral hydrate.

Chronic poisoning may manifest with symptoms of gastritis, skin rash, peripheral vasodilation, hypotension, renal damage and myocardial depression.

**Treatment:** Supportive therapy includes respiratory and cardiovascular assistance and maintenance of body temperature and circulation. Gastric lavage may be indicated if performed soon after ingestion or in patients who are comatose or at risk of convulsing. The airway should be protected in obtunded or unconscious patients. Activated charcoal may be administered.

Cardiac monitoring is important, especially in patients with pre-existing cardiac disease. Hypotension should be treated with appropriate i.v. fluids and electrolytes; dopamine or norepinephrine may be required. Baseline hepatic and renal function tests should be obtained.

Hemodialysis removes both the parent drug and the trichloroethanol metabolite.

**Dosage:** Dosage must be individualized. Doses for oral and rectal routes are equivalent. Chloral hydrate can be administered rectally by moistening capsules or as a retention enema by dissolving liquid in cottonseed or olive oil or in a hydrophillic polyethylene glycol base.

Capsules should be taken with a full glass (240 mL) of water, milk, fruit juice or ginger ale; they must not be crushed or chewed. The liquid formulation should be diluted with approximately 120 mL of water or other liquid to reduce gastric irritation.

Chloral hydrate should be avoided in patients with moderate to severe renal failure (creatinine clearance <0.8 mL/s), or in patients with severe hepatic dysfunction. No dosage adjustment is necessary for patients with mild renal failure.

**Hypnotic:** Adults: 500 to 1000 mg, 15 to 30 minutes before bedtime.
Geriatrics: Initial 250 mg, 15 to 30 minutes before bedtime.

Children: 50 mg/kg at bedtime, maximum 1 000 mg per single dose.

Sedative: Adults: 250 mg 3 times daily after meals, maximum 2 000 mg/day.

Children: 25 mg/kg/day divided into 3 to 4 doses (after meals), maximum 500 mg/dose.

Premedicant: Adults: 500 to 1 000 mg, 30 minutes prior to procedure.

Children: 25 to 50 mg/kg, 30 minutes prior to procedure. May repeat in 30 minutes using half the dose. Maximum 1 000 mg per single dose.

Ethanol Withdrawal: For management of withdrawal symptoms, a dose of 500 mg to 1 g, repeated at 6-hour intervals, has been used. Single or daily dose should not exceed 2 g.