

Product Information

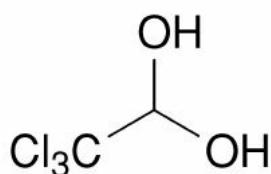
Chloral Hydrate Mixture 1g/10mL

Name of Drug:

Chloral hydrate

Description:

Chloral hydrate is a 2,2,2- trichloroethane-1,1-diol.



$C_2H_3Cl_3O_2$. MW = 165.4
CAS Number = 302-17-0

Chloral hydrate occurs as colourless, transparent crystals with an aromatic, penetrating, and slightly acrid odour. It is very soluble in water and freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Chloral hydrate volatilises slowly on exposure to air and should be stored in airtight containers.

Excipients:

Sucrose, citric acid anhydrous, sodium citrate, saccharin sodium, glycerol, methyl hydroxybenzoate, ethanol, propylene glycol, peppermint oil, purified water.

Pharmacology:

Chloral hydrate is a hypnotic and sedative with CNS depressant properties similar to barbiturates. The mechanism of action of the drug is not completely known, however the CNS depressant effects of chloral hydrate are believed to be mainly due to the active metabolite trichloroethanol.

Pharmacokinetics:

Absorption: Chloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral administration. The duration of action is for between 4-8 hours. Plasma concentrations of chloral hydrate (or the major metabolite trichloroethanol) required for sedative or hypnotic effects are unknown.

Distribution: Chloral hydrate is widely distributed throughout the body, as is the active metabolite trichloroethanol. Both have been detected in the CSF, umbilical cord blood, foetal blood, and amniotic fluid. The active metabolite is 70% to 80% protein bound. Following therapeutic doses of chloral hydrate, only small amounts of the clinically active metabolite are distributed into breast milk.

Metabolism: Chloral hydrate is rapidly metabolised by the liver, erythrocytes and other tissues to form trichloroethanol (an active metabolite). The reduction of chloral hydrate to trichloroethanol is catalysed by alcohol dehydrogenase and other enzymes. The plasma half life of trichloroethanol is about 4-12 hours. This is increased to 1-2 days in neonates. A small but variable amount of chloral hydrate and a larger portion of trichloroethanol are oxidised to trichloroacetic acid (an inactive metabolite) in the liver and kidneys. Trichloroethanol may also be conjugated to form trichloroethanol glucuronide, another inactive metabolite.

Excretion: The metabolites of chloral hydrate are slowly excreted in the urine. Some metabolites may also be excreted into the bile and faeces. Chloral hydrate is not excreted in the urine unchanged. The quantities of metabolites excreted in the urine may vary between individuals, as well as in the same individual on different days.

Indications:

Chloral Hydrate Mixture is indicated pre-operatively to produce sedation. It is also indicated for short term (not more than 2 weeks) use as a hypnotic to assist in sleep disorders.

Contra-indications:

Chloral hydrate is contraindicated in patients with:

- Marked hepatic or renal impairment
- Severe cardiac disease
- Gastritis, oesophagitis or gastric or duodenal ulcers
- Porphyrias
- Previous history of a hypersensitivity reaction to chloral hydrate itself, or to any of the excipients contained in the mixture

Chloral hydrate is also contraindicated for sedation of children with obstructive sleep apnoea, due to the risk of life threatening respiratory obstruction.

Precautions:

Alertness: Chloral hydrate may impair mental and/or physical abilities, and may cause drowsiness which may persist the next day. Patients should therefore be cautioned about performing activities requiring mental alertness or physical coordination (e.g. operating machinery or driving).

Dependence: Tolerance to chloral hydrate may develop and dependence may occur. Chloral hydrate should therefore be used with caution in patients who are mentally depressed, have suicidal tendencies, or a history of drug or alcohol abuse. Tolerance and psychologic dependence may develop by the second week of continued therapy. Individuals dependent on chloral hydrate may take large dosages of the drug, and fatalities have occurred.

Withdrawal: Withdrawal symptoms, similar to those of barbiturates, can occur if chloral hydrate is stopped abruptly. These symptoms can include delirium tremens (sometimes fatal) and hallucinations. Prolonged administration and abrupt withdrawal of chloral hydrate should therefore be avoided to prevent precipitation of withdrawal symptoms. Dependent persons should be hospitalised, and the drug withdrawn slowly.

Chronic Toxicity: Prolonged administration of chloral hydrate may result in adverse reactions including gastritis, skin eruptions or parenchymatous renal damage.

Porphyria: Chloral hydrate should not be used in patients with porphyria (see **Contraindications**). The drug has been reported to precipitate attacks of acute, intermittent porphyria.

Respiratory Disease: As with all sedatives, chloral hydrate should be used with caution in those with respiratory insufficiency.

Sleep Apnoea: Children with sleep apnoea, particularly obstructive sleep apnoea with tonsillar hypertrophy, could be at risk of life threatening respiratory obstruction if chloral hydrate is used for sedation (see **Contraindications**).

Gastric Irritation: Chloral hydrate is irritating to the skin and mucous membranes. Gastric irritation may be minimised by diluting the oral solution with water, or other liquids.

Use in Children and Infants: Deaths have occurred prior to or following diagnostic procedures, particularly in paediatric patients, after chloral hydrate was administered to induce sedation before the procedure. Chloral hydrate should be administered only at the health care facility, where appropriate monitoring can be instituted. Monitoring must continue until the child meets appropriate discharge criteria. In addition, particular care must be taken in calculating and administering the proper dose appropriate to the age and weight of paediatric patients.

The half life of trichloroethanol, an active metabolite of chloral hydrate, is prolonged in neonates. Repeated administration in infants and children may lead to accumulation of metabolites and

thereby increase the potential for excessive CNS depression, predispose neonates to conjugated and non-conjugated hyperbilirubinaemia, decrease albumin binding of bilirubin, and contribute to metabolic acidosis. Chloral Hydrate Mixture is not recommended in infants and children when repetitive dosing would be necessary.

Use in the Elderly: The dose of chloral hydrate may need to be reduced in the elderly due to age related decreases in both hepatic and renal function (see also **Contraindications**). Delirium may occur when chloral hydrate is used in conjunction with psychotropic or cholinergic drugs.

Hepatic and Renal Impairment: The dose of chloral hydrate may need to be reduced.

Use in Pregnancy: Category A Chloral hydrate should be used in pregnancy only when clearly needed. Chloral hydrate crosses the placenta and chronic use during pregnancy may cause withdrawal symptoms in the neonate.

Australian categorisation definition of *Category A*:
Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Use in Lactation:

Chloral hydrate is distributed into breast milk and may lead to sedation in breast-fed infants.

Carcinogenicity, Mutagenicity, Impairment in Fertility:

Data on the long-term safety of chloral hydrate are incomplete. Long-term use of chloral hydrate is not recommended.

Interactions with Other Drugs:

CNS depressants

Additive CNS depression may occur when chloral hydrate is administered concomitantly with other CNS depressants such as alcohol, antihistamines, barbiturates, opiates, antipsychotics, tricyclic antidepressants, and other sedatives.

Delirium may occur, especially in the elderly, when chloral hydrate is used in conjunction with psychotropic or anticholinergic drugs.

In addition, patients receiving chloral hydrate may develop a vasodilation reaction characterised by tachycardia, palpitations, facial flushing, and dysphoria after ingesting alcohol. If chloral hydrate is used concomitantly with other depressant drugs including alcohol, caution should be used to avoid overdose.

Coumarin anticoagulants

Chloral hydrate may produce a transient increase in the hypoprothrombinemic response to warfarin. Trichloroacetic acid, a major metabolite of chloral hydrate, appears to displace warfarin bound plasma proteins, resulting in a transient increase in unbound plasma warfarin concentrations.

Chloral hydrate should therefore be used with caution in patients receiving warfarin or other oral anticoagulants. Even though the interaction between chloral hydrate and warfarin does not usually cause adverse effects, it is preferable to use hypnotic drugs that do not appear to interact with anticoagulants.

When chloral hydrate is given to a patient receiving an oral anticoagulant, the patient should be monitored for excessive hypoprothrombinaemia during the first several days of chloral hydrate therapy. The long-term co-administration of the 2 drugs probably does not increase the risk of bleeding significantly.

Intravenous frusemide

A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given intravenous (IV) frusemide subsequent to chloral hydrate. Symptoms reported included diaphoresis, flushes, variable blood pressure including

hypertension, and uneasiness. Therefore, it may be preferable to use an alternative hypnotic drug in patients who require IV frusemide

Effects on Laboratory Tests:

Chloral hydrate may interfere with tests for urinary glucose which use copper sulphate, such as Clinitest[®]. Urinary glucose tests which utilise glucose oxidase, such as Clinistix[®], are not affected, and should be used when patients are receiving chloral hydrate.

Chloral hydrate may also interfere with fluorometric tests for determining urine catecholamines. Chloral hydrate should not be used for 48 hours preceding the test.

Tests for determining 17-hydroxycorticosteroids, such as Reddy, Jenkins and Thorn procedure, may also be affected by chloral hydrate.

Adverse Reactions: Below are some of the reactions that have been reported.

Gastrointestinal: The most frequent adverse effects of chloral hydrate is gastric irritation in the form of nausea and vomiting. Diarrhoea, flatulence, unpleasant taste and abdominal distension occurs less frequently.

Central Nervous System: Residual sedation or hangover occurs infrequently following usual hypnotic doses. Occasionally, patients may become somnambulist, disoriented, incoherent and display paranoid behaviour. Rarely, paradoxical excitement, hallucinations, nightmares, delirium, staggering gait, ataxia, light-headedness, headache, vertigo, dizziness, drowsiness, and confusion have occurred.

Dermatological: Cutaneous reactions to chloral hydrate are not common but have included scarlatiniform or erythematous rash, urticaria, angioedema, purpura, eczema, bullous lesions, and erythema multiforme.

Haematological: Leukopenia and eosinophilia have occasionally been reported. Chloral hydrate has also been reported to precipitate attacks of acute intermittent porphyria (see **Precautions**).

Miscellaneous:

Ketonuria has been reported rarely with chloral hydrate.

Additional effects including coma, hypotension, hypothermia, respiratory depression and cardiac arrhythmias have occurred with high doses (see **Overdose**).

Dosage and Administration:

The dosage of chloral hydrate must be individualised for each patient.

Generally Chloral Hydrate Mixture should be well diluted with water or another liquid (e.g. fruit juice, ginger ale) prior to administering. Gastric irritation may be minimised by diluting the mixture before administering.

Adults:

The usual hypnotic dose is 500mg to 1g given 15-30 minutes before bedtime, or when used as a preoperative medication, 30 minutes before surgery.

The maximum daily dose in adults should not exceed 2g.

Children:

Sedatives should be administered preoperatively to children only at the health facility, where appropriate monitoring can be instituted (see **Precautions**). Monitoring must continue until the child's level of consciousness has returned to a state that meets the approved discharge criteria.

Particular care must be taken in calculating and administering the proper dose appropriate to the age and weight of paediatric patients.

The usual hypnotic dose is 30-50 mg/kg or 1.5 g/m² with a maximum single dose of 1g (10mL).

As premedication, children have been given chloral hydrate in a dose of 20-50 mg/kg, to a maximum single dose of 1g.

Hepatic or Renal Impairment:

The dosage in these patients may need to be reduced (see **Precautions and Contraindications**).

Elderly or Debilitated:

The dosage in these patients may need to be reduced (see **Precautions**).

Overdosage:

Symptoms: The symptoms of overdosage with chloral hydrate resemble barbiturate overdose. Significant toxicity usually develops within 2 to 3 hours of ingestion. Symptoms include coma, hypotension, hypothermia, respiratory depression, and cardiac arrhythmias. Miosis, vomiting, and muscle flaccidity may also occur. Oesophageal stricture, gastric necrosis and perforation, and GI haemorrhage have also been reported. Hepatic and renal function may be impaired and may result in transient jaundice and/or albuminuria. Renal tubular toxicity may occur between 2 and 5 days following ingestion.

Death may result from respiratory failure, cardiac arrest or hypotension.

Significant toxicity has occurred in children with ingestion of 1.5g. The lethal oral dose of chloral hydrate in adults is about 10g; however, ingestion of 4g has caused death, and some patients have survived ingestion of as much as 30g.

Treatment: General symptomatic and supportive treatment, including maintenance of airway, assisted respiration, oxygen administration, and maintaining body temperature and circulation, should be administered as appropriate. Continuous cardiac monitoring is important, especially in patients with predisposing cardiac disease.

Activated charcoal has been recommended within one hour of ingestion, provided the airway can be protected. Haemodialysis reportedly enhances the elimination of trichloroethanol.

Presentation

AUST R 42850: Chloral Hydrate Mixture 1g/10mL, is a clear, colourless, syrupy liquid in a 200mL bottle.

Storage:

Store below 25°C
Protect from light.

Schedule:

All States and A.C.T. - S.4. (Prescription Only Medicine)

Sponsor:

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