

Preparations

BP 2008: Clomethiazole Capsules; Clomethiazole Intravenous Infusion; Clomethiazole Oral Solution.

Proprietary Preparations (details are given in Part 3)

Austral.: Heminevin; **Belg.:** Distaneurine; **Cz.:** Heminevin; **Denm.:** Heminevin; **Fin.:** Heminevin; **Ger.:** Distaneurin; **Gr.:** Distaneurine; **Hong Kong:** Heminevin; **Hung.:** Heminevin; **Irl.:** Heminevin; **Norw.:** Heminevin; **Pol.:** Heminevin; **Spain:** Distaneurine; **Swed.:** Heminevin; **Switz.:** Distaneurin; **UK:** Heminevin.

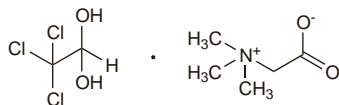
Cloral Betaine (BAN, rINN)

Chloral Betaine (USAN); Cloral betaina; Cloral Bétaine; Cloralum Betainum; Compound 5107. An adduct of cloral hydrate and betaine.

Хлораль Бетайн

$C_7H_{12}Cl_3NO_3 \cdot H_2O = 282.5$.

CAS — 2218-68-0.



Profile

Cloral betaine rapidly dissociates in the stomach to release cloral hydrate and has actions and uses similar to those of cloral hydrate (below). It is given orally in the short-term management of insomnia (p.957), as tablets containing 707 mg (equivalent to about 414 mg of cloral hydrate). The usual hypnotic dose is one or two tablets taken at night with water or milk. The maximum daily dose is five tablets (equivalent to about 2 g of cloral hydrate). A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Somnwell; Welldorm.

Cloral Hydrate

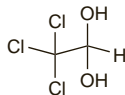
Chloral Hydrate (BAN); Chloral, hydrate de; Chloralhydrát; Chlorali hydras; Chloralio hidratas; Chloralu wodzian; Cloral, hidrató de; Kloraalihydraatti; Kloral Hidrat; Klorál-hidrat; Kloralhydrat. 2,2,2-Trichloroethane-1,1-diol.

$C_2H_3Cl_3O_2 = 165.4$.

CAS — 302-17-0.

ATC — N05CC01.

ATC Vet — QN05CC01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cloral hydrate: Jellies; Jelly beans; Joy Juice; Knockout Drops; Knock out Drops; Mickey; Mickey's; Mickey Finn; Mickey Finns; Peter; Torpedo.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Chloral Hydrate). Colourless, transparent crystals. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Chloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acid odour. It volatilises slowly on exposure to air and melts at about 55°. Soluble 1 in 0.25 of water, 1 in 1.3 of alcohol, 1 in 2 of chloroform, and 1 in 1.5 of ether; very soluble in olive oil. Store in airtight containers.

Incompatibility. Cloral hydrate is reported to be incompatible with alkalis, alkaline earths, alkali carbonates, soluble barbiturates, borax, tannin, iodides, oxidising agents, permanganates, and alcohol (cloral alcoholate may crystallise out). It forms a liquid mixture when triturated with many organic compounds, such as camphor, menthol, phenazone, phenol, thymol, and quinine salts.

Dependence and Withdrawal, Adverse Effects, and Treatment

Cloral hydrate has an unpleasant taste and is corrosive to skin and mucous membranes unless well diluted. The most frequent adverse effect is gastric irritation; abdominal distension and flatulence may also occur. CNS effects such as drowsiness, light-headedness, ataxia, headache, and paradoxical excitement, hallucinations, nightmares, delirium, and confusion (sometimes with paranoia) occur occasionally. Hypersensitivity reactions include skin rashes (erythema multiforme and Stevens-Johnson syndrome have been reported with the related compound triclofos). Ketouria may occur.

The effects of acute overdosage resemble acute barbiturate intoxication (see Amobarbital, p.962 and below), and are managed similarly. In addition the irritant effect may cause initial vomiting, and gastric necrosis leading to strictures. Cardiac arrhythmias have been reported. Jaundice may follow liver damage, and albuminuria may follow kidney damage.

Tolerance may develop and dependence may occur. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Incidence of adverse effects. In a drug surveillance programme,¹ adverse effects of cloral hydrate, which were reversible, occurred in 2.3% of 1130 patients evaluated and included gastrointestinal symptoms (10 patients), CNS depression (20), and skin rash (5). In 1 patient the prothrombin time was increased; in 1 patient hepatic encephalopathy seemed to worsen; and bradycardia developed in 1 patient. In another such programme, adverse effects occurred in about 2% of 5435 patients given cloral hydrate.² Three reactions were described as life-threatening.

1. Shapiro S, *et al.* Clinical effects of hypnotics II: an epidemiologic study. *JAMA* 1969; **209**: 2016–20.
2. Miller RR, Greenblatt DJ. Clinical effects of cloral hydrate in hospitalized medical patients. *J Clin Pharmacol* 1979; **19**: 669–74.

Carcinogenicity. Cloral hydrate has been widely used as a sedative, especially in children. Concern over warnings that cloral hydrate was carcinogenic in *rodents*¹ has prompted some experts, including the American Academy of Pediatrics, to review the relative risks of the medical use of this drug.^{2,3} The original warnings appear to have been based, in part, on the assumption that cloral hydrate was a reactive metabolite of trichloroethylene and was responsible for its carcinogenicity, but there is evidence to suggest that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite. Studies *in vitro* indicate that cloral hydrate can damage chromosomes in some mammalian test systems but there have been no studies of the carcinogenicity of cloral hydrate in humans. Some long-term studies in *mice* have linked cloral hydrate with the development of hepatic adenomas or carcinomas. However, it was noted that cloral hydrate was not the only sedative that had been shown to be a carcinogen in experimental *animals*. The American Academy of Pediatrics considered cloral hydrate to be an effective sedative with a low incidence of acute toxicity when given short-term as recommended and, although the information on carcinogenicity was of concern, it was not sufficient to justify the risk associated with the use of less familiar sedatives. There was no evidence in infants or children showing that any of the available alternatives were safer or more effective. However, the use of repetitive dosing with cloral hydrate to maintain prolonged sedation in neonates and other children was of concern because of the potential for accumulation of drug metabolites and resultant toxicity. A recent cohort study⁴ found no persuasive evidence to support a relationship between the use of cloral hydrate and the development of cancer. However, the statistical power was low for weak associations, particularly for some individual cancer sites.

1. Smith MT. Cloral hydrate warning. *Science* 1990; **250**: 359.
2. Steinberg AD. Should cloral hydrate be banned? *Pediatrics* 1993; **92**: 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of cloral hydrate for sedation in children. *Pediatrics* 1993; **92**: 471–3.
4. Haselkorn T, *et al.* Short-term cloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29**: 67–77.

Effects on the CNS. A 2-year-old child¹ had the first of 2 seizures 60 minutes after receiving cloral hydrate 70 mg/kg for sedation.

1. Muñoz M, *et al.* Seizures caused by cloral hydrate sedative doses. *J Pediatr* 1997; **131**: 787–8.

Hyperbilirubinaemia. Small retrospective studies¹ have suggested that prolonged use of cloral hydrate in neonates may be associated with the development of hyperbilirubinaemia. This may possibly be related to the prolonged half-life of the metabolite trichloroethanol in neonates.

1. Lambert GH, *et al.* Direct hyperbilirubinaemia associated with cloral hydrate administration in the newborn. *Pediatrics* 1990; **86**: 277–81.

Overdosage. The general management of poisoning with cloral hydrate resembles that for barbiturates (see Treatment of Adverse Effects, under Amobarbital, p.962). Activated charcoal may be given orally to adults and children within 1 hour of ingestion of more than 30 mg/kg, provided that the airway can be protected; the value of gastric decontamination for overdose is uncertain. Of 76 cases of cloral hydrate poisoning reported to the UK National Poisons Information Service (NPIS), 47 were severe.¹ Of 39 adults, 12 had cardiac arrhythmias including 5 with cardiac arrest. Antiarrhythmic drugs were recommended unless obviously contra-indicated. Haemoperfusion through charcoal or haemodialysis was recommended for patients in prolonged coma. Cardiac arrhythmias and CNS depression were also major features of 12 cases of cloral hydrate overdose reported from Australia.² Lidocaine was not always successful in controlling arrhythmias, but propranolol was successful in all 7 patients in whom it was used. It was noted that resistant arrhythmias, particularly ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, were the usual cause of death in patients who had taken an overdose of cloral hydrate. Although

there had been no controlled studies of antiarrhythmic therapy in overdose with cloral hydrate, the successful use of beta blockers appeared to be a recurring feature in reports in the literature. Indeed, the UK NPIS notes that tachyarrhythmias usually respond readily to an intravenous beta blocker such as esmolol or propranolol.

Giving flumazenil produced an increased level of consciousness, pupillary dilatation, and return of respiratory rate and blood pressure towards normal in a patient who had taken an overdose of cloral hydrate.³

1. Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *BMJ* 1978; **2**: 960.
2. Graham SR, *et al.* Overdose with chloral hydrate: a pharmacological and therapeutic review. *Med J Aust* 1988; **149**: 686–8.
3. Donovan KL, Fisher DJ. Reversal of chloral hydrate overdose with flumazenil. *BMJ* 1989; **298**: 1253.

Precautions

Cloral hydrate should not be used in patients with marked hepatic or renal impairment or severe cardiac disease, and oral dosage is best avoided in the presence of gastritis. As with all sedatives, it should be used with caution in those with respiratory insufficiency.

Cloral hydrate can cause drowsiness that may persist the next day; affected patients should not drive or operate machinery. Prolonged use and abrupt withdrawal of cloral hydrate should be avoided to prevent precipitation of withdrawal symptoms. Repeated doses in infants and children may lead to accumulation of metabolites and thereby increase the risk of adverse effects. Use is best avoided during pregnancy.

Cloral hydrate may interfere with some tests for urinary glucose or 17-hydroxycorticosteroids.

Breast feeding. The American Academy of Pediatrics¹ states that, although usually compatible with breast feeding, use of cloral hydrate by breast-feeding mothers has been reported to cause sleepiness in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 28/04/04)

Neonates. The half-life of trichloroethanol, an active metabolite of cloral hydrate, is prolonged in neonates;¹ values of up to 66 hours have been reported in some studies. Short-term sedation in the neonate with single oral doses of 25 to 50 mg/kg of cloral hydrate is considered¹ to be probably relatively safe, but repeated dosage carries the risk of accumulation of metabolites which may result in serious toxicity. Toxic reactions may occur even after the drug has been stopped since the metabolites may accumulate for several days.

1. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31**: 423–43.

Obstructive sleep apnoea. Children with obstructive sleep apnoea could be at risk from life-threatening respiratory obstruction if cloral hydrate is used for sedation. Details of 2 such children who suffered respiratory failure after sedation with cloral hydrate for lung function studies have been reported.¹

1. Biban P, *et al.* Adverse effect of cloral hydrate in two young children with obstructive sleep apnea. *Pediatrics* 1993; **92**: 461–3.

Porphyria. UK licensed product information recommends that cloral hydrate should not be used in patients with porphyria, although some¹ consider it safe; caution would seem appropriate.

1. Welsh Medicines Information Centre. Drugs that are considered to be safe for use in acute porphyrias. Available at: <http://www.wmic.wales.nhs.uk/pdfs/porphyria/PorphyriaSafeList.pdf> (accessed 24/06/08)

Interactions

The sedative effects of cloral hydrate are enhanced by other CNS depressants such as alcohol (the 'Mickey Finn' of detective fiction), barbiturates, and other sedatives.

Cloral hydrate may alter the effects of coumarin anticoagulants (see Warfarin, p.1430). A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given an intravenous dose of furosemide subsequent to cloral hydrate.

Pharmacokinetics

Cloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral doses. It is widely distributed throughout the body. It is rapidly metabolised to trichloroethanol and trichloroacetic acid (p.1620) in the erythrocytes, liver, and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide (urochlorallic acid) and as trichloroacetic acid. Some is also excreted in the bile.

Trichloroethanol is the active metabolite, and passes into the CSF, into breast milk, and across the placenta. The half-life of trichloroethanol in plasma is reported to range from about 7 to 11 hours but is considerably prolonged in the neonate. Trichloroacetic acid has a plasma half-life of several days.

Uses and Administration

Cloral hydrate is a hypnotic and sedative with properties similar to those of the barbiturates. It is used in the short-term management of insomnia (p.957) and has been used for sedation and as a sedative for premedication (p.1780); its use as a hypnotic, particularly in children, is now limited. It has been widely used for