Clomethiazole *(BAN, rINN)*

Chlormethiazole; Clométhiazole; Clomethiazolum; Clometiazol; Klometiatsoli; Klometiazol. 5-(2-Chloroethyl)-4-methyl-1,3-thiazole.

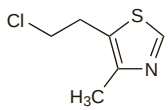
Клометиазол

C_6H_8ClNS = 161.7.

CAS — 533-45-9.

ATC — N05CM02.

ATC Vet — QN05CM02.



Pharmacopoeias. In *Br.*

BP 2008 (Clomethiazole). A colourless to slightly yellowish-brown liquid with a characteristic odour. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. A 0.5% solution in water has a pH of 5.5 to 7.0. Store at a temperature of 2° to 8°.

Clomethiazole Edisilate *(BANM, rINNM)*

Chlormethiazole Edisylate; Chlormethiazole Ethanedisulphonate; Clométhiazole, Edisilate de; Clomethiazole Edisylate *(USAN)*; Clomethiazoli Edisilas; Edisilato de clometiazol; Klometiazolu edysylan; NEX-002. 5-(2-Chloroethyl)-4-methylthiazole ethane-1,2-disulphonate.

Клометиазола Эдизилат

$(C_6H_8ClNS)_2,C_2H_6O_6S_2$ = 513.5.

CAS — 1867-58-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Clomethiazole Edisilate). A white crystalline powder with a characteristic odour. Freely soluble in water; soluble in alcohol; practically insoluble in ether.

Incompatibility. Several studies have shown that clomethiazole edisilate may permeate through or be sorbed onto plastics used in intravenous infusion bags or giving sets.[1-4] The drug may also react with and soften the plastic.[1] The manufacturers of clomethiazole edisilate have suggested that thrombophlebitis, fever, and headache reported in young children during prolonged infusions may have been due to reaction with plastic giving sets and silastic cannulae. Recommendations for intravenous use have therefore included the use of a motor-driven glass syringe in preference to a plastic drip set in small children, changing plastic drip sets at least every 24 hours when used in older patients, and use of teflon intravenous cannulas.

1. Lingam S, *et al.* Problems with intravenous chlormethiazole (Heminevrin) in status epilepticus. *BMJ* 1980; **280:** 155–6.
2. Tsuei SE, *et al.* Sorption of chlormethiazole by intravenous infusion giving sets. *Eur J Clin Pharmacol* 1980; **18:** 333–8.
3. Kowaluk EA, *et al.* Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J Pharm Sci* 1984; **73:** 43–7.
4. Lee MG. Sorption of four drugs to polyvinyl chloride and polybutadiene intravenous administration sets. *Am J Hosp Pharm* 1986; **43:** 1945–50.

Dependence and Withdrawal

Dependence may develop, particularly with prolonged use of higher than recommended doses of clomethiazole. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Adverse Effects, Treatment, and Precautions

Clomethiazole may produce nasal congestion and irritation, sneezing, and conjunctival irritation sometimes associated with a headache. Nasopharyngeal or bronchial secretions may be increased. Skin rashes and urticaria have also occurred and in rare cases bullous eruptions have been reported. Gastrointestinal disturbances including nausea and vomiting, have been reported after oral doses. Reversible increases in liver enzyme values and blood-bilirubin concentrations have also been noted. Clomethiazole can cause excessive drowsiness, particularly in high doses; drowsiness may persist the next day, and patients affected should not drive or operate machinery. Paradoxical excitation or confusion may occur rarely. Anaphylaxis has also been reported rarely.

Excessive doses may produce coma, respiratory depression, hypotension, and hypothermia; pneumonia may follow increased respiratory secretion. Treatment is as for barbiturate overdose (see Amobarbital, p.962).

Clomethiazole is contra-indicated in patients with acute pulmonary insufficiency, and should be given with care to patients with sleep apnoea syndrome, chronic pulmonary insufficiency, or renal, liver, cerebral, or cardiac disease. Clomethiazole should be given with caution to elderly patients as there may be increased bioavailability and delayed elimination. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome.

Administration by intravenous infusion. Severe adverse effects have followed the intravenous use of clomethiazole, and intravenous preparations are no longer generally available. Facilities for intubation and resuscitation were required when clomethiazole was given intravenously, with care taken to ensure that the patient's airway was maintained since there is a risk of mechanical obstruction during deep sedation. At too high a rate of infusion, sleep induced with clomethiazole could lapse into deep unconsciousness and patients required close and constant observation. Rapid infusion has also caused transient apnoea and hypotension, and special care was needed in patients susceptible to cerebral or cardiac complications, including the elderly. With prolonged infusion there was also a risk of electrolyte imbalance due to the water load involved with the glucose vehicle. Recovery has been considerably delayed after prolonged infusion.

Effects on the heart. Cardiac arrest in 2 chronic alcoholics might have been associated with clomethiazole infusion.[1]

1. McInnes GT, *et al.* Cardiac arrest following chlormethiazole infusion in chronic alcoholics. *Postgrad Med J* 1980; **56:** 742–3.

Overdosage. A report of clomethiazole poisoning on 16 occasions in 13 patients, some of whom had also taken other drugs and alcohol.[1] There was increased salivation on 7 occasions; otherwise the clinical features were those of barbiturate poisoning (see Adverse Effects of Amobarbital, p.962). The highest plasma-clomethiazole concentration was 36 micrograms/mL, with the highest value in a conscious patient 11.5 micrograms/mL. All the patients survived following intensive supportive treatment as for barbiturate poisoning.

1. Illingworth RN, *et al.* Severe poisoning with chlormethiazole. *BMJ* 1979; **2:** 902–3.

Parotitis. Acute bilateral parotitis has been reported in a patient given clomethiazole.[1] The swelling disappeared after withdrawal of clomethiazole and recurred on rechallenge.

1. Bosch X, *et al.* Parotitis induced by chlormethiazole. *BMJ* 1994; **309:** 1620.

Pregnancy. There have been reports of neonates being adversely affected by clomethiazole given to their mothers for toxaemia of pregnancy.[1,2] Effects included sedation, hypotonia, and apnoea. In a report[1] it was suggested that the effects might have been due to a synergistic interaction between clomethiazole and diazoxide as these drugs were given to most of the mothers with affected infants.

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* 1976; **1:** 943.
2. Wood C, Renou P. Sleepy and hypotonic neonates. *Med J Aust* 1978; **2:** 73.

Interactions

The sedative effects of clomethiazole are enhanced by CNS depressants such as alcohol, barbiturates, other hypnotics and sedatives, and antipsychotics.

Alcohol. Although clomethiazole has been a popular choice for the treatment of alcohol withdrawal symptoms (p.1626), if it is given long-term, patients readily transfer dependency to it; if they also continue to abuse alcohol this may lead to severe self-poisoning with deep coma and potentially fatal respiratory depression.[1]

1. McInnes GT. Chlormethiazole and alcohol: a lethal cocktail. *BMJ* 1987; **294:** 592.

Beta blockers. Sinus bradycardia developed in an 84-year-old woman taking *propranolol* for hypertension 3 hours after she took a second dose of clomethiazole 192 mg.[1] Her pulse rate increased on stopping propranolol and clomethiazole and later stabilised when she took propranolol with haloperidol.

1. Adverse Drug Reactions Advisory Committee (Australia). *Med J Aust* 1979; **2:** 553.

Diazoxide. For a report of adverse reactions in neonates born to mothers given clomethiazole and diazoxide, see Pregnancy under Adverse Effects, Treatment, and Precautions, above.

Histamine H_2-antagonists. A study of the pharmacokinetics of clomethiazole edisilate 1 g orally in 8 healthy subjects, before and after doses of *cimetidine* 1 g daily for 1 week, showed that mean clearance of clomethiazole was reduced by 31% by cimetidine.[1] This was associated with an increase in the mean peak plasma concentration of the hypnotic from 2.664 to 4.507 micrograms/mL and an increase in the mean elimination half-life from 2.33 to 3.63 hours. After the original dose of clomethiazole subjects slept for 30 to 60 minutes, whereas after cimetidine, most slept for at least 2 hours.

Ranitidine did not significantly affect the pharmacokinetics of clomethiazole in a study in 7 healthy subjects.[2]

1. Shaw G, *et al.* Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* 1981; **21:** 83–5.
2. Mashford ML, *et al.* Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* 1983; **34:** 231–3.

Pharmacokinetics

Clomethiazole is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 15 to 90 minutes after oral doses depending on the formulation used. It is widely distributed in the body and is reported to be 65% bound to plasma proteins. Clomethiazole is extensively metabolised, probably by first-pass metabolism in the liver with only small amounts appearing unchanged in the urine. The elimination half-life has been reported to be about 4 hours but this may be increased to 8 hours or longer in the elderly or in patients with hepatic impairment. Clomethiazole crosses the placenta and is distributed into breast milk.

Hepatic impairment. Studies in 8 patients with advanced cirrhosis of the liver and in 6 healthy men showed that the amount of unmetabolised clomethiazole reaching the circulation after an oral dose was about 10 times higher in the patients than in the controls.[1] Low concentrations in the controls were related to extensive first-pass metabolism in the liver.

1. Pentikäinen PJ, *et al.* Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. *Eur J Clin Pharmacol* 1980; **17:** 275–84.

Uses and Administration

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is used orally in the treatment of agitation and restlessness (see Disturbed Behaviour, p.954) in elderly patients, in the short-term management of severe insomnia (p.957) in the elderly, and in the treatment of acute alcohol withdrawal symptoms (p.1626). It was also given as an intravenous infusion in the management of status epilepticus (p.469) and impending or actual eclampsia (p.470); however, a parenteral formulation of clomethiazole no longer appears to be available.

In the UK, clomethiazole (as *Heminevrin*; *AstraZeneca*) is available as capsules containing 192 mg of clomethiazole base and as syrup containing 250 mg of the edisilate in 5 mL. As a result of differences in the bioavailability of these preparations, 192 mg of the base in the capsules is considered therapeutically equivalent to 250 mg (5 mL) of the edisilate in the syrup, i.e. one capsule or 5 mL of syrup are equivalent in their effects.

The usual hypnotic dose of clomethiazole for **insomnia** is 1 or 2 capsules (192 or 384 mg of the base) or the equivalent. For **restlessness and agitation** in the elderly 1 capsule (192 mg of the base), or the equivalent dose as one of the other dosage forms, may be given 3 times daily.

Various clomethiazole regimens have been suggested for the treatment of **alcohol withdrawal**, usually starting with 9 to 12 capsules, or the equivalent, divided into 3 or 4 doses, on the first day, and gradually reducing the dosage over the next 5 days. Treatment should be carried out in hospital or in specialist centres, and use for longer than 9 days is not recommended because of the risk of dependence (see above).

Porphyria. Clomethiazole is one of the drugs that has been used for seizure prophylaxis in patients with porphyria (p.471) who continue to experience convulsions while in remission.

Stroke. Clomethiazole has been studied[1,2] as a neuroprotective drug in the acute management of patients with stroke, but no beneficial effect on long-term outcome was found.

1. Wahlgren NG, *et al.* CLASS Study Group. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke* 1999; **30:** 21–8.
2. Lyden P, *et al.* Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke* 2002; **33:** 122–8.

Substance dependence. For a discussion of the management of *opioid* withdrawal symptoms, including mention of the use of clomethiazole, see p.101.

Preparations

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

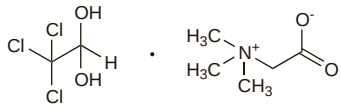
Proprietary Preparations (details are given in Part 3)
Austral.: Heminevrin; ***Belg.:*** Distraneurine†; ***Cz.:*** Heminevrin; ***Denm.:*** Heminevrin; ***Fin.:*** Heminevrin†; ***Ger.:*** Distraneurin; ***Gr.:*** Distraneurine; Heminevrin; ***Hong Kong:*** Heminevrin†; ***Hung.:*** Heminevrin; ***Irl.:*** Heminevrin; ***Norw.:*** Heminevrin; ***Pol.:*** Heminevrin; ***Spain:*** Distraneurine; ***Swed.:*** Heminevrin; ***Switz.:*** Distraneurin; ***UK:*** Heminevrin.

Cloral Betaine *(BAN, rINN)*

Chloral Betaine *(USAN)*; Cloral betaína; Cloral Bétaïne; Cloralum Betainum; Compound 5107. An adduct of cloral hydrate and betaine.

Хлораль Бетаин

$C_7H_{12}Cl_3NO_3,H_2O$ = 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.

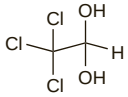
Preparations

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, hidrato de; Kloraalihydraatti; Kloral Hidrat; Klorál-hidrát; 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; Mickeys; Mickey Finn; Mickey Finns; Peter; Torpedo.

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

Ph. Eur. 6.2 (Cloral 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 (Cloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid 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, lightheadedness, 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). Ketonuria 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 chloral 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 study[4] 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. Chloral hydrate warning. *Science* 1990; **250:** 359.
2. Steinberg AD. Should chloral hydrate be banned? *Pediatrics* 1993; **92:** 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993; **92:** 471–3.
4. Haselkorn T, *et al*. Short-term chloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29:** 67–77.

Effects on the CNS. A 2-year-old child[1] 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 chloral hydrate sedative doses. *J Pediatr* 1997; **131:** 787–8.

Hyperbilirubinaemia. Small retrospective studies[1] 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 hyperbilirubinemia associated with chloral 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 overdosage 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 overdosage of cloral hydrate. Although there had been no controlled studies of antiarrhythmic therapy in overdosage 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 overdosage 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 Pediatrics[1] 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 considered[1] 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 chloral 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 some[1] 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 (urochloralic 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