Chloral Hydrate

Newborn use only

2021

Alert	High risk medicine: risk of causing significant patient harm when used in error. Chloral hydrate should be given by medical personnel in healthcare environment only. Osmolality is 3285 mOsm/kg of water.
Indication	Sedation for diagnostic/non-painful procedure (e.g. neuroimaging, echocardiography, Brainstem auditory evoked potentials (BERA)).(1-4) Sedative/hypnotic for short-term use.
Action	Pure sedative-hypnotic drug without analgesic properties.(4) Exact mechanism of sedation is not yet known. Chloral hydrate is metabolised to trichloroethanol (TCE), which is responsible for the majority of the sedative-hypnotic effect.(5)
Drug type	Sedative and hypnotic drug.
Trade name	Orion Chloral Hydrate Mixture (Perrigo Australia)
Presentation	Chloral Hydrate Mixture 1 g/10 mL (100 mg/mL) oral liquid, 200 mL
Dose	25 mg/kg/dose (20-50 mg/kg/dose) (1, 4, 5) For non-painful procedure – administer 30 minutes before the procedure. Do not exceed a total of 50 mg/kg prior to the procedure For sedation in ICU – Avoid repeated and/or prolonged doses. Avoid giving at less than 6 hourly intervals. Not to exceed 100 mg/kg/day. Note: Tolerance may develop after prolonged regular use. **Preterm neonates:** Avoid any repeat doses in preterm infants and neonates < 7 days old.
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – Reduce dose in mild impairment and avoid in significant impairment. Hepatic impairment – Reduce dose in mild impairment and avoid in significant impairment.
Maximum dose	50 mg/kg per procedure
Total cumulative dose	100 mg/kg/day
Route	Oral or gastric.
Preparation	Syrup – 100 mg/mL (osmolality is 3285 mOsm/kg of water). Oral preparation should be diluted 1:3-1:5 with sterile water or administered after feeding to reduce gastric irritation.
Administration	
Monitoring	Observe for respiratory depression, apnoea, bradycardias, hypotension. In preterm infants up to 44 weeks corrected age - observations should continue for at least 24 hours after dose administration.(1) Residual agitation may occur for several hours.(4)
Contraindications	Significant hepatic and/or renal disease. Severe cardiac disease. Gastritis, oesophagitis or gastric or duodenal ulcers. Porphyrias. Obstructive sleep apnoea. Previous history of hypersensitivity reaction to chloral hydrate or to any of the excipients.
Precautions	Reduce dose in mild hepatic and renal impairment. Avoid prolonged use and abrupt withdrawal thereafter. Administration with other CNS depressants such as opioids, benzodiazepines or barbiturates may produce excessive sedation. Indirect hyperbilirubinaemia may occur after prolong use because TCE and bilirubin compete for hepatic conjugation. Use cautiously in preterm infants due to the risk of respiratory depression.
Drug interactions	Additive effect with opioids, barbiturates, benzodiazepines leading to respiratory depression. May produce a transient increase in response to warfarin due to displacement of warfarin from its protein binding site. Avoid concomitant use of furosemide – intravenous furosemide after chloral hydrate has been reported to produce diaphoresis, flushing, changes in blood pressure and tachycardia in adults and older children. May displace phenytoin from protein binding sites and reduce its rate of elimination.

Adverse reactions	Respiratory depression and bradycardia. Gastric irritation with nausea and vomiting. Reduced oral intake.(1) In premature infants , episodes of bradycardia may occur for up to 24 hours after a dose.(1) Hyperbilirubinemia. Metabolic acidosis (from accumulation of the metabolite, trichloroacetic acid). Paradoxical excitement may occur. Tolerance with prolonged administration. Prolonged administration or acute overdose can cause neurologic, respiratory and myocardial depression; cardiac arrhythmia and bladder atony. Serious adverse events including death/permanent neurologic injury have been reported in children in a review of adverse event care reports from the adverse drug reporting system of the Food and Drug Administration, the US Pharmacopoeia, and the results of a survey of paediatric specialists.(6)
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Not applicable.
Storage	Store below 25°C. Protect from light.
Excipients	Sucrose, citric acid, sodium citrate, saccharin sodium, glycerol, methyl hydroxybenzoate, ethanol 2.4% v/v, propylene glycol, natural peppermint flavour and purified water.
Special comments	Chloral hydrate has no analgesic properties, excitement may occur in patients with pain. Despite being restricted in some countries (e.g. France) as a result of potential carcinogenicity, the American Academy of Pediatrics has judged the evidence insufficient to avoid single doses of chloral hydrate for this reason alone.(4, 7)
Evidence	**Efficacy** Chloral hydrate is effective for sedation for painless procedures in children.(2, 8)(Level II, Grade C). The data in neonates are insufficient to promote the regular use of chloral hydrate as a sedative for neonates in intensive care.(9) (Level III, Grade C). **Dosing:** There is paucity of information regarding dosage and dosing intervals in neonates. The suggested dose in this formulary was based on 2 prospective observational clinical and pharmacologic evaluation of chloral hydrate in neonates.(1, 5) Allegaert et al showed achievement of adequate sedation for BERA (Brainstem auditory evoked potentials) with 30 mg/kg/dose of chloral hydrate in preterm infants. Increased sedation was observed up to 12 hours after the administration. They noted apnoeic and bradycardic episodes both before and after chloral hydrate administration in these infants, but the frequency and duration of bradycardic episodes were more for up to 24 hours after chloral hydrate. Reimche et al administered 20-50 mg/kg/dose of chloral hydrate with repeat doses at 6-24 hour intervals and achieved adequate sedation and improvement in irritability in neonates without any significant impact on blood pressure, heart rate and respiratory rate.(5) Alternative doses, e.g. 8-10 mg/kg/dose have been suggested but not substantiated by any evidence. **Dilution:** Medications added to milk feeds have the potential to raise osmolality, causing feed intolerance and necrotizing enterocolitis.(10) It is recommended to calculate the diluent volume to keep the osmolality ≤ 450 mOsm/kg.(10-12) **Safety** Chloral hydrate in preterm infants can cause post-procedural bradycardic events and decreased oral intake in the 24 hour interval period after the administration.(1) Trichlorethanol (TCE) and trchloroacetic acid (TCA), active metabolites of chloral hydrate were detected in blood up to 84 hours in neonates on chloral hydrate. Indirect bilirubin was significantly elevated suggesting TCE actively competes with bilirubin for glucuronidation in liver.(5) Prolonged use warrants monitoring of serum bilirubin level.(5) Chloral hydrate overdose may produce cardiac arrhythmias including torsades de pointes.(13) There are no studies pertaining to chloral hydrate associated carcinogenicity in humans.(7) Death/severe permanent neurologic injuries have been reported in children, with sedatives in non-hospital based settings, particularly when the sedatives were given by health professionals not trained in advanced resuscitation skills.(6) **Pharmacokinetics** Chloral hydrate is rapidly and effectively absorbed via the oral route and is immediately metabolised by liver enzymes (alcohol dehydrogenase) to the active hypnotic metabolite trichloroethanol (TCE). It is

	eventually excreted in the urine after glucuronidation in the liver. Plasma concentration peaks within 30 minutes to an hour. It is also metabolised to trichloroacetic acid (TCA). Both TCE (8–64 hours) and TCA (days) have long plasma half-lives in neonates and accumulate with repeated doses.(5)
Practice points	
References	1. Allegaert K, Daniels H, Naulaers G, Tibboel D, Devlieger H. Pharmacodynamics of chloral hydrate in former preterm infants. European journal of pediatrics. 2005;164(7):403-7. 2. D'AGOSTINO J, TERNDRUP TE. Chloral hydrate versus midazolam for sedation of children for neuroimaging: a randomized clinical trial. Pediatric emergency care. 2000;16(1):1-4. 3. Hijazi OM, Ahmed AE, Anazi JA, Al-Hashemi HE, Al-Jeraisy MI. Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. Saudi Med J. 2014;35(2):123-31. 4. Krauss B, Green SM. Procedural sedation and analgesia in children. The Lancet. 2006;367(9512):766-80. 5. Reimche L, Sankaran K, Hindmarsh K, Kasian G, Gorecki D, Tan L. Chloral hydrate sedation in neonates and infants-clinical and pharmacologic considerations. Developmental pharmacology and therapeutics. 1989;12:57-64. 6. Coté CJ, Notterman DA, Karl HW, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. Pediatrics. 2000;105(4):805-14. 7. American academy of pediatrics. Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. Pediatrics. 1993;92(3):471. 8. Wheeler DS, Jensen RA, Poss WB. A randomized, blinded comparison of chioral hydrate and midazolam sedation in children undergoing echocardiography. Clinical pediatrics. 2001;40(7):381-7. 9. Cruise S, Tam-Chan D, Harrison D, Johnston L. Prospective clinical audit of chloral hydrate administration practices in a neonatal unit. Journal of paediatrics and child health. 2012;48(11):1010-5. 10. Chandran S, Chua MC, Lin W, Wong JM, Saffari SE, Rajadurai VS. Medications that increase osmolality and compromise the safety of enteral feeding in preterm infants. Neonatology. 2017;111(4):309-16. 11. Barness LA, Mauer AM, Holliday MA, Anderson AS, Dallman PR, Forbes GB, et al. Commentary on breast-feeding and infant formulas, including proposed standards for formulas. Pediatrics. 1976;57(2):278-85. 12. Kreissl A, Zwiauer V, Repa A, Binder C, Haninger N, Jilma B, et al. Effect of fortifiers and additional protein on the osmolarity of human milk: is it still safe for the premature infant? Journal of pediatric gastroenterology and nutrition. 2013;57(4):432-7. 13. Pershad J, Palmisano P, Nichols M. Chloral hydrate: the good and the bad. Pediatric emergency care. 1999;15(6):432-5.

VERSION/NUMBER	**DATE**
Original 1.0	24/08/2016
Revised 2.0	**22/03/2021**
Current 3.0	**16/09/2021**
REVIEW	16/09/2026

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