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The Use of Chloral Hydrate in Infants and Children

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Chloral hydrate was introduced into medical use by Liebreich in 1869 as the first synthetic sedative-hypnotic. Unlike opioids, it produces sedation without significant adverse effects on cardiovascular or respiratory function at therapeutic doses. As early as 1894, chloral hydrate was being used in children.[1] Despite the availability of newer agents, chloral hydrate remains a common choice. In a 2003 survey of pediatric critical care fellowship training programs in the United States, chloral hydrate was the seventh most frequently used drug for sedation and analgesia.[2] This issue of *Pediatric Pharmacotherapy* will review the pharmacology of chloral hydrate and describe recent studies of its use in infants and children.

Use in Infants and Children

Chloral hydrate produces effective sedation in 80 to 90% of patients. It is often selected because of the availability of an oral dosage form and its relatively mild adverse effect profile. Unfortunately, its unpredictable onset, long duration, and the lack of a reversal agent, make chloral hydrate less than an ideal sedative.[1-4]

There are a large number of studies examining the utility of chloral hydrate for procedural sedation. In the past decade, most have focused on unique patient populations or have used chloral hydrate as a standard for comparison to other sedatives.[5-8] One of the largest studies was published in 1996 by Napoli and colleagues.[5] The population consisted of 405 children (3 weeks to 14 years of age) undergoing echocardiography. The average dose of chloral hydrate was 77 mg/kg, with a range of 25 to 125 mg/kg. Effective sedation was achieved in 98% of the children, with 82% of patients achieving sedation within 30 minutes. Two percent failed to achieve sedation. Children 3 years of age or younger were more likely to be successfully sedated than older children. None of the children had a clinically significant change in heart rate or blood pressure; however, oxygen saturation decreased in 6%. This was more common in children with trisomy 21. Vomiting occurred in 6% of the patients. The authors concluded that chloral hydrate was a safe and effective agent for this patient population.

In 2000, the efficacy of chloral hydrate was compared to midazolam in a study by D'Agostino and Terndrup.[6] Forty children (2 months to 8 years of age) were randomized to receive a single oral dose of either 75 mg/kg of chloral hydrate or 0.5 mg/kg midazolam prior to outpatient neuroimaging. The study was stopped after 33 children had completed the protocol, due to the high failure rate. Efficacy was significantly better in the chloral hydrate group (100% of patients completed the scan versus 50% of the midazolam patients). The need for supplementary dosing was also lower in the chloral hydrate group (9% versus 55%). Mean duration of sedation was not significantly different, and no adverse effects were noted.

The following year, Wheeler and colleagues conducted another randomized, blinded comparison of chloral hydrate and midazolam for procedural sedation.[7] A total of 40 children under 5 years of age undergoing echocardiography were given either 75 mg/kg chloral hydrate or 0.5 mg/kg midazolam. There was no difference in mean time for onset of sedation between chloral hydrate (25.0 ± 4.7 minutes) and midazolam (27.3 ± 2.9 minutes). Mean time to recovery was significantly shorter with midazolam (37.4 ± 3.4 minutes compared to 80.6 ± 15.6 minutes for chloral hydrate). The level of sedation was significantly deeper with chloral hydrate. Successful sedation, as determined by a standardized score, was achieved in 93% of the chloral hydrate patients compared to only 36% of the midazolam group. No adverse events were reported in either group.

A retrospective study published by Mason in 2003 compared pentobarbital to chloral hydrate for sedation of infants undergoing magnetic resonance imaging or computed tomographic studies.[8] The authors reviewed the records of 1,393 cases (1,024 pentobarbital cases and 374

chloral hydrate cases). The median dose was 4 mg/kg pentobarbital and 50 mg/kg chloral hydrate. There were no significant differences between the groups in mean time to sedation (18±11 minutes for pentobarbital and 17±12 minutes for chloral hydrate) or time to discharge (102±34 minutes versus 103±36 minutes). Average duration of sedation was approximately 85 minutes in both groups. There were significantly fewer adverse effects in the pentobarbital group (0.5 versus 2.7%). This resulted from patients in the chloral hydrate group experiencing more episodes of oxygen desaturation. The authors concluded that the medications were equally effective, but that pentobarbital was better tolerated.

Mechanism and Pharmacokinetic Profile

Chloral hydrate may be administered orally or rectally. It is rapidly absorbed and widely distributed throughout the body. Chloral hydrate is rapidly converted to trichloroethanol (TCE), the primary active metabolite. The formation of TCE results from reduction of chloral hydrate by alcohol dehydrogenase in the liver and erythrocytes. TCE is further metabolized by glucuronide conjugation to form urochloralic acid and by oxidation to trichloroacetic acid (TCA). This latter compound may also be formed from oxygenation of chloral hydrate, itself. TCE and its conjugated forms are excreted into the urine and, to a lesser extent, the bile. The elimination half-life of TCE in adults is 7 to 10 hours, while TCA is eliminated much more slowly, with a half-life of 67 hours.[1,3,9]

Both chloral hydrate and TCE cause a nonspecific depression of the central nervous system. The exact mechanism of this effect is not yet known. Given the rapid metabolism of chloral hydrate, TCE is considered to produce the sedative activity associated with this drug. It has been suggested that TCE concentrations greater than 10 mcg/ml are adequate to produce sedation.[1,3,9]

The pharmacokinetic profile of chloral hydrate has been studied in infants and children. Gershanik and colleagues reported that peak TCE concentrations of 10-55 mcg/ml occurred 1 to 12 hours after a single chloral hydrate dose in neonates.[10] Concentrations rose to as high as 70 mcg/ml after repeated dosing. The average elimination half-life was 37.3 hours (range 8.5-64 hours), considerably longer than in adults.

Reimche and coworkers conducted a study in 12 infants who received at least six oral chloral hydrate doses of 20 to 50 mg/kg.[11] In samples collected after the last dose, the average TCE concentration was 46.2±24.1 mcg/ml, with a range of 13.3 to 88.8 mcg/ml.

Mayers and colleagues investigated the disposition of a single 50 mg/kg oral dose of chloral hydrate in 22 infants and young children.[12] Peak concentrations of TCE declined with increasing age: 36.28±10.65 mcg/ml in preterm infants, 28.23±9.36 mcg/ml in term infants, and 27.06±10.36 mcg/ml in children 1 to 13 years of age. Mean time to peak TCE concentrations ranged from 2.23 to 5.02 hours. A significant relationship was found between age and TCE half-life. In the preterm infants, the average half-life was 39.82±14.27 hours, compared to 27.80±21.32 hours in the term infants, and 9.67±1.72 hours in the older infants and children.

Drug Interactions

The administration of chloral hydrate with other central nervous system depressants, such as opioids, benzodiazepines, or barbiturates, may produce excessive sedation. In the intensive care setting, where patients are frequently given multiple sedatives, the repeated use of chloral hydrate should be closely monitored.[1,3,9]

Chloral hydrate may produce a transient increase in response to warfarin, resulting in a hypoprothrombinemic effect. This reaction appears to result from displacement of warfarin from its protein binding sites, resulting in a higher concentration of free drug. This interaction appears to become less pronounced with long-term administration.[1,3,9]

Administration of intravenous furosemide after chloral hydrate has been reported to produce diaphoresis, flushing, alterations in blood pressure, and tachycardia. While most frequently reported in adults, Dean and colleagues reported similar symptoms in an 8 year old boy receiving nightly chloral hydrate during mechanical ventilation.[13] Over a two day period, the child received five doses of furosemide. Each was given less than 24 hours after a dose of chloral hydrate. After each dose, the patient experienced diaphoresis, flushing, agitation, and tachycardia. Symptoms began within 5 minutes and lasted 15 to 20 minutes, resolving without intervention.

The mechanism of this interaction is believed to be related to the displacement of TCA from its albumin binding sites by furosemide. The resulting unbound TCA may produce the symptoms observed. It has also been suggested that free TCA may displace thyroxine from thyroid-binding proteins, with the resulting symptoms produced by unbound thyroxine.[13]

It has been suggested that chloral hydrate may displace phenytoin from protein binding sites and reduce its rate of elimination. While this interaction has not been well studied, phenytoin concentrations should be monitored in patients receiving these agents concomitantly.[1,3,9]

Adverse Effects

With single-dose or short-term use, chloral hydrate is well tolerated by most patients. The most common adverse effects reported include mild respiratory depression, nausea and vomiting in 4 to 15% of children, and prolonged drowsiness, disorientation, confusion, headache, or lethargy occurring in up to 30%. Paradoxical agitation has been reported in 2 to 6% of pediatric patients.[1,3-5,8,9]

Less frequently reported reactions to chloral hydrate include nightmares or hallucinations, hypersensitivity reactions (rash, urticaria, and erythema), perioral skin and mucosal lesions, hepatic dysfunction, leukopenia, eosinophilia, hypotension, dyspnea, bradycardia, and seizures. In addition, there have been isolated reports of chloral hydrate-induced obstructive apnea, acute laryngeal edema, and acute laryngospasm. These cases may reflect irritation of the mucosa following aspiration of chloral hydrate syrup.[1,3,9]

Hyperbilirubinemia has been reported in infants receiving chloral hydrate. It has been suggested that that the TCA metabolite may displace bilirubin from its albumin binding sites. This adverse effect has not been well studied, but warrants monitoring of serum bilirubin in infants receiving long-term therapy.[1,3,9]

Following an overdose of chloral hydrate, symptoms may include vomiting, stupor, coma, pinpoint pupils (followed by dilation as coma progresses), hypotension, respiratory depression, and hypothermia. In addition, gastric strictures, gastric perforation and necrosis, and hemorrhagic gastritis may occur. Jaundice and renal dysfunction associated with albuminuria have also been reported. Management of overdose may include gastric decontamination, supportive care, and hemoperfusion.[1,3,9]

Chloral hydrate overdose may also produce supraventricular, junctional, and ventricular arrhythmias, including torsades de pointes. Although generally believed to have little effect on the heart in therapeutic doses, arrhythmias have also been reported after routine use in infants and children.[13,14] Arrhythmias may result from alterations in the automaticity of pacemaker cells by chloral hydrate metabolites or sensitization to catecholamines. Suppression may be accomplished with lidocaine, phenytoin, and beta-adrenergic blocking agents.[1,3,9]

Despite the relative safety of chloral hydrate, all patients should be appropriately monitored for cardiovascular and respiratory changes. In their evaluation of 95 cases of adverse events associated with procedural sedation, Coté and colleagues found that chloral hydrate was the drug most frequently associated with adverse events occurring outside the hospital setting.[16] Seven of the 15 cases resulted in death or neurologic injury. In five of the cases, chloral hydrate was the only drug administered. Four of the seven cases involved an overdose.

Potential as a Carcinogen

In a letter to the editor published in *Science* in 1990, Smith first called attention to the chromosome-damaging properties of chloral hydrate and the potential for carcinogenicity in the pediatric population given this medication.[17] The author cited studies in mice that documented the development of hepatic adenomas or carcinomas. Chloral hydrate has been shown *in vitro* to have an adverse effect on mitosis, resulting in cell mutation.

At this time, there have been no reports of cancer in humans attributed to the use of chloral hydrate. After weighing the available evidence from laboratory studies, the American Academy of Pediatrics issued a policy statement in 1993 stating that chloral hydrate remained an acceptable option for short-term sedation.[18] Subsequent studies have provided additional support for its safety.[19] While there may be little harm with the use of single doses for procedural sedation, prolonged administration in the intensive care setting should be carefully considered in light of this potential risk, particularly in premature neonates who may have an impaired ability to eliminate the potentially toxic metabolites.[18,20]

Dosing Recommendations

For sedation prior to medical procedures in infants and children, the recommended dose of chloral hydrate is 50 to 75 mg/kg given orally or rectally. In more recent studies, higher single doses of up to 100 mg/kg have been used with increased success in children and infants over 1 month of age.[20] A larger single dose may minimize the development of paradoxical excitation. Although a maximum dose for pediatric patients has not been established, 2 grams has been suggested as an upper limit. For infants and young children, the maximum dose should be 1 gram.[1,3,9,21,22]

Chloral hydrate dosing for sedation during mechanical ventilation is less well established. Doses of 10 to 50 mg/kg are typically given every 6 to 8 hours. Treatment of premature neonates should begin at the lower end of the range to account for their slower elimination.[1,3,9]

Because of the renal excretion of chloral hydrate metabolites, it should not be used repeatedly in patients with moderate to severe renal impairment. Chloral hydrate should not be used in patients with hepatic dysfunction, due to reduced efficacy and the potential to adversely affect the metabolism of other drugs.[1,3,9]

Tolerance and Dependence

The prolonged administration of chloral hydrate may lead to the development of tolerance and physiologic dependence. Although documented more frequently in adults, this has also been reported in infants and children receiving chloral hydrate for prolonged periods. Symptoms of withdrawal are similar to those seen with alcohol withdrawal, including paradoxical agitation, anxiety, and tremor. In patients with tolerance, discontinuation of therapy should be done through gradual dose reduction. A regimen of a 10% reduction every 1 to 2 days has been used successfully to prevent withdrawal.[1,3,9]

Availability

Chloral hydrate is available in 500 mg capsules, 50 mg/ml and 100 mg/ml syrups, and 324 and 648 mg suppositories. It is available through a variety of manufacturers. The syrup dosage form is bitter tasting. Administration with milk or juice may improve palatability.[1,3,9]

Summary

Although chloral hydrate was first introduced into pediatric practice over a century ago, it remains a popular option for the sedation. In the past decade, several new publications have confirmed its efficacy, increased our knowledge of its disposition and pharmacokinetics, and reexamined its adverse effect profile in children. This new information may be very helpful when determining the appropriate place for chloral hydrate in current clinical practice.

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There was no Pharmacy and Therapeutics Committee meeting in August.

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