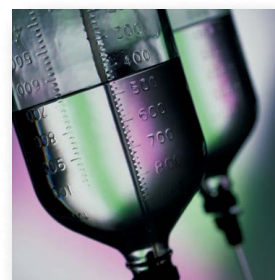


Chloral Hydrate: Is It Still Being Used? Are There Safer Alternatives?

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Problem

Among the classes of the high-alert medications is one that includes minimal and moderate sedation agents. These comprise medications used to sedate pediatric patients for diagnostic tests or procedures in various settings, such as radiology, electrocardiography, neurologic testing labs, dentistry, the emergency department (ED), and the operating room. Sedating pediatric patients even for painless diagnostic procedures is common because the practice has been linked to higher quality studies and reduced diagnostic errors.¹

The pediatric oral sedation agent provided as an example on our ISMP List of High-Alert Medications in Acute Care Settings and ISMP List of High-Alert Medications in Community/Ambulatory Healthcare is oral chloral hydrate, a sedative-hypnotic that has been used for more than 100 years.²

Older Chloral Hydrate Adverse Events

Between 1996 and 2009, ISMP published dozens of reports on errors surrounding the use of chloral hydrate for sedation; mostly, these involved dosing errors, oversedation, and administration of the oral liquid by the intravenous (IV) route. The events we published included eight that had resulted in death. In two cases, technical support personnel, who were unauthorized to administer the drug, failed to recognize that they were administering an overdose. In the third fatality, a dentist ordered a weight-based dose of 6,000 mg chloral hydrate for a 13-year-old child that led to respiratory arrest. In three more cases, the drug was administered to a child by a parent at home, prior to a procedure. In

two of those cases, the drug had been prescribed by volume alone, and the pharmacy dispensed a higher concentration of the commercial product than that intended by the prescriber (500 mg/5 mL instead of 250 mg/5 mL), which led to an overdose in both cases. In the other case, the pharmacy dispensed a 10-fold overdose. Yet another case involved a 4-year-old boy who was given chloral hydrate before a procedure and strapped onto a papoose board without his head being properly positioned to protect his airway. The final reported fatality was caused by repeated “5 mL PRN” doses that led to the patient’s respiratory arrest.

Compounded Chloral Hydrate

Since 2010, ISMP has received no additional reports of errors involving pediatric sedation with chloral hydrate. We assumed this was largely due to the 2012 discontinuation of the only remaining commercially available chloral hydrate products in the U.S. (oral solution by Pharmaceutical Associates and oral capsules by Breckenridge) for business reasons.³ However, some ambulatory and hospital pharmacies are still compounding an oral suspension of chloral hydrate from crystals or powder for pediatric sedation in both the inpatient and outpatient setting.^{4,5} The raw ingredient is available from pharmaceutical supply companies. A study⁵ comparing the previously available commercial formulation of chloral hydrate with the compounded formulation used for pediatric sedation during an echocardiographic examination showed that the compounded drug resulted in a shorter duration of sedation, more frequent need for a secondary sedation agent (thereby increasing the risk of an adverse event^{4,6}), and more frequent sedation failure.

There are no Food and Drug Administration (FDA)-approved drug products that contain chloral hydrate. As mentioned above, the firms that were commercially manufacturing and distributing drug products containing

chloral hydrate, without FDA approval, voluntarily removed their products from the market in 2012. We had considered removing chloral hydrate from the ISMP lists of high-alert medications but have not done so given the unknown frequency with which the drug is prescribed and compounded. More recently, there have also been worrisome adverse events associated with the drug as reported by the news media and in professional literature. Chloral hydrate has a U.S. Pharmacopeial Convention (USP) monograph so pharmacists can compound it under section 503A (individual prescription) of the Federal Food, Drug, and Cosmetic (FD&C) Act, but it can’t be compounded under 503B (outsourcing facilities) because it is *not* on the FDA’s list of bulk drug substances.

Recent Chloral Hydrate Adverse Events

In June 2014, Nordt et al. published three cases of pediatric chloral hydrate overdoses, including one fatality, that occurred in the outpatient setting following procedural sedation.² These patients were all seen in the ED within a four-month period, which alerted the authors to a potential public safety issue.

The first case involved a 4-year-old girl for whom a dentist had prescribed 900 mg (70 mg/kg) of chloral hydrate prior to a dental extraction. The child was sedated upon her arrival at the office, and the procedure was completed without further sedation. After an hour, the patient remained somnolent but arousable and was discharged. The child’s mother called six hours later to report ongoing somnolence and was reassured that the effects of sedation would decrease over time. Several minutes later, the child suffered a respiratory arrest and the mother called emergency medical services. The resuscitation efforts pre-hospital and in the ED were extensive, and there was an initial return of spontaneous circulation. But the child arrested again and died.

The next event involved a 3-year-old boy for whom a dentist had prescribed 500 mg (50 mg/kg) of chloral hydrate to

be administered at home prior to arrival at the office for a dental procedure. (Only healthcare professionals should administer sedatives to children before a procedure *after* they have arrived at the facility; this helps ensure proper supervision, monitoring, and access to resuscitation equipment and other medications, if needed.) The dentist had anticipated repeat visits and prescribed 60 mL of chloral hydrate (100 mg/mL). The child's mother could speak Spanish and English, but could read only Spanish, so she asked a family member to read the label. That person mistakenly directed her to give the child the entire 60 mL (6,000 mg) bottle. Within 10 minutes, the child became somnolent and was unresponsive by the time he was in the dental office. The mother alerted the office staff, who called emergency medical services. The child vomited on the way to the ED, where he was intubated and treated with an esmolol infusion for life-threatening cardiac dysrhythmias. He was admitted to a pediatric intensive care unit and discharged 24 hours later without sequelae.

The third event involved a 15-month-old child with a history of severe neurodevelopmental deficits who was given 1,200 mg chloral hydrate (100 mg/kg) at an outpatient ophthalmology clinic prior to evaluation. Within 25 minutes of receiving the drug, the child vomited, became obtunded, and developed stridor, periods of apnea, and cyanosis. The child improved after an oral airway was established and oxygen was administered, whereupon she was transferred to the ED, monitored for 12 hours, and then discharged.

Other Issues with Chloral Hydrate

In addition to the risk of respiratory depression that is associated with most sedatives used for pediatric sedation, chloral hydrate carries several other risks that are worth mentioning:

Resedation after discharge. Chloral hydrate can result in prolonged sedation or resedation, with effects that persist beyond 24 hours in children of all ages, including those who have demonstrated resolution of sedation prior to discharge.^{2,4,7} This appears to have played a role in the fatality of the 4-year-old girl described previously. Chloral hydrate is rapidly converted to an active metabolite (trichloroethanol) that is responsible

for its sedative properties; at therapeutic doses, it has a half-life of up to 66 hours in neonates, 28 to 40 hours in infants, 8 to 12 hours in children, and a much longer half-life following an overdose.^{2,7}

No reversal agent. If respiratory depression occurs or if the patient becomes obtunded, there is no specific agent available to reverse the effects of chloral hydrate.²

Narrow therapeutic index. Chloral hydrate has a relatively narrow therapeutic index, which can increase the risk of adverse effects when higher doses, or overdoses, are administered.²

Cardiac toxicity and hypotension. Ventricular dysrhythmias and severe hypotension, which has led to some fatalities, from chloral hydrate toxicity have been reported. These effects were observed mostly after large doses or overdoses, as they are dose-dependent.^{2,8}

Irritating gastric effects. Nordt et al. note that chloral hydrate is more rapidly absorbed with food; fasting before a procedure where chloral hydrate is used for sedation is not recommended as it can delay the drug's onset, leading to sedation failure.² However, gastric irritation has caused vomiting, which can result in the aspiration of stomach contents.

Large volume per dose. Chloral hydrate is very bitter tasting and each dose requires a large volume. Poor palatability has sometimes necessitated its administration via a nasogastric tube.⁹ In addition, compounded chloral hydrate is difficult to concentrate, which leads to even larger volumes per dose than the previously available commercial formulation.⁵ This can result in the patient vomiting or spitting out unquantifiable amounts of the dose.

Comparison to Other Pediatric Sedation Agents

Chloral hydrate has been the drug of choice for pediatric sedation in some facilities because of its low cost.⁵ However, concerning its efficacy, there are conflicting studies regarding which sedation agent is best. Numerous studies suggest that there are many other effective sedative agents with more predictable pharmacokinetic profiles than chloral hydrate, including oral or intranasal midazolam.^{6,7,10-12} Other studies have shown that the use of chloral hydrate resulted in more effective sedation of pediatric

patients than other agents,^{9,13-15} and recommendations for its continued use for certain procedures exist in the literature, particularly for painless diagnostic procedures such as neurologic imaging,^{13,16} echocardiography,⁵ and auditory brainstem response testing.¹⁷

Nevertheless, many other studies have shown that other sedation agents, such as midazolam, produce less severe adverse effects. For example, Costa et al. studied pediatric patients who received a high dose of either oral chloral hydrate (70-100 mg/kg) or oral midazolam (1-1.5 mg/kg) during outpatient dental treatment. They found that the chance of an adverse event occurring, including post-discharge, was significantly lower among children who received midazolam than among those who received chloral hydrate.⁷ Cote et al. found that, among 118 cases of serious (neurologic injury) or fatal outcomes reported to the FDA, most of the children (65%) had been sedated with chloral hydrate.⁶

CONCLUSION

The risk of adverse events and the potential for compounding errors associated with chloral hydrate are of great concern. Thus, the literature is replete with recommendations to use a safer, alternative agent when sedating pediatric patients.^{2,4,6,7,10-12,18-19} However, evidence regarding the efficacy of chloral hydrate and of alternative sedatives is conflicting.

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