J. Med. Toxicol. (2014) 10:219–222
DOI 10.1007/s13181-013-0358-z

TOXICOLOGY OBSERVATION

Pediatric Chloral Hydrate Poisonings and Death Following Outpatient Procedural Sedation

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Published online: 15 February 2014

Abstract
Introduction Chloral hydrate has been used medicinally since the 1800 s as a sedative hypnotic, most commonly for procedural sedation. As it is administered orally and available in a liquid formulation, it is used almost exclusively in pediatric patients despite many safer and more effective alternative agents being available.
Case Series We present three cases of pediatric chloral hydrate poisoning, all occurring following procedural sedation in outpatient clinic settings and presenting to the emergency department. The ages ranged from 15 months to 4 years of age and all required resuscitation. Unfortunately, the 4-year-old died.
Conclusion Choral hydrate is associated with significant adverse effects, including death, and safer alternatives for pediatric procedural sedation should be sought and utilized. There are a number of more effective sedative agents with more predictable pharmacokinetic and safety profiles than chloral hydrate including parenteral and oral agents. The practice of pre-procedure sedation should be performed only in a supervised setting where cardiorespiratory monitoring can occur in all cases.

Keywords Chloral hydrate · Trichloroethanol · Procedural sedation · Conscious sedation · Pediatrics

Introduction

Chloral hydrate has been used for over 100 years in medicine as a sedative hypnotic, including for procedural sedation [1, 2]. As it is administered orally and is available in liquid formulation, it is used almost exclusively in pediatric patients despite many safer and more effective alternative agents being available. Chloral hydrate is absorbed from the gastrointestinal tract with peak serum concentrations within 30 to 60 min [2]. Chloral hydrate is rapidly converted in vivo to the pharmacologically active metabolite, trichloroethanol (TCE), which is responsible for the sedative properties [2].

A common unsafe practice for outpatient procedural sedation is to have the caregiver administer a dose of chloral hydrate at home before the procedure with the expectation that the patient will be sedated upon arrival to the facility where the procedure will occur. This is particularly commonplace in outpatient settings, e.g., dental procedures, pediatric echocardiography, magnetic resonance imaging, and also in some emergency departments. This is concerning as there is no monitoring en route and is not recommended. We present three cases of chloral hydrate pediatric poisonings, all occurring in outpatient clinical settings following procedural sedation. These three cases all occurred within a 4-month period independent of each other alarming us of a potential serious public healthcare issue. We performed bedside consultations on each child at our respective institutions, two presented to a

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tertiary children's hospital and the other to a large county pediatric emergency medicine department.

Case 1

A 4-year-old girl weighing 12.8 kg was prescribed chloral hydrate 900 mg (70 mg/kg) by her dentist, given orally at home prior to a dental extraction. The patient was fasting as instructed for the procedure. She was sedated upon arrival at the office and underwent a successful tooth extraction without any additional sedation. After the procedure and an observation period of approximately 1 h, she remained somnolent but was arouseable and discharged to home. The mother called the office 6 h following the procedure to report she was still somnolent and was reassured that effects would decrease over time. Approximately 5 min later, she found her unresponsive and not breathing. Paramedics were called and found her pulseless and initiated cardiopulmonary resuscitation (CPR) and administered intramuscular epinephrine per paramedic protocol. In the emergency department (ED), she had a Glasgow coma score (GCS) of 3 and was asystolic. An arterial blood gas (ABG) revealed serum pH of 6.54, pCO2 of 70, pO2 of 271, and with a base excess of −32.9. She underwent emergent rapid sequence intubation (RSI) immediately upon arrival with continued CPR. Rapid sequence intubation involved the immediate administration of a sedating medication to induce anesthesia followed by a skeletal muscle paralytic agent and then endotracheal intubation. She received a total of nine doses of epinephrine in addition to doses of atropine and sodium bicarbonate intravenously. There was return of spontaneous circulation but with persistent hypotension requiring both dopamine and epinephrine infusions. A repeat ABG showed minimal improvement of serum pH to 7.06 with a pCO2 to 51, pO2 to 312, and a decrease in base excess to −16. She was transferred to a tertiary children's hospital pediatric intensive care unit (PICU). On arrival, she was unresponsive on a ventilator with GCS 3 with pupils fixed and dilated without any sedation. Initial vital signs in the PICU demonstrated a heart rate of 155 bpm with a blood pressure of 76/38 mmHg on dopamine and epinephrine infusions. Over the next 12 h, she remained unchanged until blood pressure slowly declined despite high doses of vasopressors. The patient had another episode of cardiopulmonary arrest and could not be successfully resuscitated. She was pronounced dead approximately 12 h after arrival. A postmortem examination revealed no structural abnormalities. Whole blood postmortem toxicology analysis identified trichloroethanol qualitatively. Measurement of the quantitative trichoroethanol (TCE) concentrations was not performed by the coroner's office.

Case 2

A 3-year-old boy weighing 10 kg was prescribed chloral hydrate 500 mg (50 mg/kg) prior to arriving for a dental procedure. The mother could speak both Spanish and English but could read only Spanish. Therefore, she was unclear about the amount of the liquid to be administered. The bottle dispensed contained 60 mL of 500 mg/5 mL chloral hydrate. She asked another family member to read the label instructions who told her to give the entire 60 mL. The total dose administered was 6,000 mg (400 mg/kg) of chloral hydrate. He became somnolent over approximately 10 min and then unresponsive after arriving at the dentist's office. The mother alerted the staff and paramedics were called. He vomited en route in the ambulance. On arrival to the ED, his vital signs revealed a heart rate of 134 bpm, blood pressure of 91/55 mmHg, oxygen saturation by bag valve mask of 98 % on 100 % oxygen. He was afebrile with a GCS 3 and emergently intubated. He had persistent sinus tachycardia in the range of 120 to 130 bpm. Cardiac monitoring demonstrated ventricular irritability with frequent bigeminy, trigeminy as well as brief runs of non-sustained ventricular tachycardia with pulses. An esmolol infusion was initiated with complete resolution of ventricular irritability and tachycardia improved to the 90- to 100-bpm range. He was admitted to the PICU and observed on an esmolol infusion. Twenty four hours following ingestion, esmolol was discontinued and he was extubated, 30 h after the ingestion. He was discharged to home without apparent neurologic sequelae.

Case 3

A 15-month-old girl weighing 12.4 kg with panhypopituitarism, hydrocephalus, with ventriculo-peritoneal shunt, and septal-optic dysplasia was given 1,200 mg chloral hydrate (100 mg/kg) at an outpatient ophthalmology clinic for sedation prior to evaluation. Vital signs following chloral hydrate administration revealed a heart rate of 133 bpm, respiratory rate of 27 bpm, blood pressure of 96/77 mmHg and oxygen saturation of 98 % on room air. Within 25 min of dosing, she vomited and had stridorous respirations with a decrease in heart rate to 101 bpm and respiratory rate of 18 bpm followed by obtundation, cyanosis, and apnea with oxygen desaturation to 64 %. Resuscitation was begun and an oral airway was placed with a non-rebreather facemask with 100 % oxygen at 15 L/min and transferred to the ED. In the ED, the oral airway was removed and replaced by a nasal trumpet as she was somnolent but not obtunded and assisted with bag–valve–mask ventilation with 100 % oxygen. As the patient was effectively being oxygenated with bag–valve ventilation and mental status was improving, endotracheal intubation was not performed. When she became more awake she was maintained on oxygen 6 L/min by

facemask. She was able to be weaned to room air over 45 min and monitored for 12 h and discharged to home without sequelae.

Discussion

Chloral hydrate is a halogenated hydrocarbon diol that has been used in medical practice since the late 1800 s [1]. It is available in both a liquid and capsule formulation with a characteristic pear-like odor [2]. Interestingly, chloral hydrate is more rapidly absorbed in the presence of food than in the fasted state [3, 4]. Therefore, fasting, which is commonly done in procedural sedation, is not recommended since it can delay onset of sedation and lead to treatment failure [1].

Usually, chloral hydrate is well absorbed from the gastrointestinal tract with peak serum concentrations within 30 to 60 min [2]. Once absorbed, chloral hydrate is rapidly converted by alcohol dehydrogenase to the compound responsible for the sedative properties, its active metabolite trichloroethanol [2]. Trichloroethanol has an elimination half-life of approximately 8 to 12 h at therapeutic doses but can be as long as 35 h following acute overdoses and poisonings. Trichloroethanol is further metabolized to an inactive metabolite, trichloroacetic acid with a half-life of over 60 h [2].

Chloral hydrate should not be used in children older than 4 years of age or in children of any age with neurodevelopmental disorders due to both increased risk of adverse events and treatment failures [1, 5, 6]. The patient in the first case presented was over 4 years of age and our third case had a history of severe neurodevelopmental deficits. Furthermore, chloral hydrate has a risk of re-sedation with effects persisting beyond 24 h in children of any age, including those who had resolution of sedation and "therapeutic" dosing [6, 7]. This appears to be what occurred in the fatality presented.

In pediatric patients, the usual dosage of chloral hydrate is 50 mg/kg to 100 mg/kg to a maximum of one gram [1, 2]. Chloral hydrate has a relatively narrow therapeutic index with the anticipated increased adverse effects with higher dosages. The second patient we presented received 1,200 mg, which is higher than the recommended dose. Obviously, the child administered the entire 60 mL (6,000 mg) and had a large overdose. The dentist who prescribed anticipated repeated visits therefore prescribed a larger quantity than usual. Inability to read prescription instructions in English has been associated with pediatric poisoning [8].

Unlike procedural sedation with benzodiazepines, where flumazenil can be used as a reversal agent when respiratory depression and obtundation occur, there is no specific reversal agent for chloral hydrate respiratory and central nervous system depression. There is a single case report of an acute chloral hydrate poisoning being reversed with flumazenil [9]. There was no determination of presence of benzodiazepines in this case report, which may have been an etiology of decreased level of consciousness. However, flumazenil has been reported to reverse other non-benzodiazepine toxins, e.g., ethanol [10]. We did not administer flumazenil to any of our patients. The administration of flumazenil, which might not be effective, could be considered particularly in patients undergoing procedural sedation as there would be little to no risk of precipitating a withdrawal syndrome.

The most worrisome adverse events from chloral hydrate use are respiratory depression and respiratory arrest. However, another potentially fatal adverse event as seen in two of the cases we presented is ventricular dysrhythmias, specifically ventricular tachycardia [11, 12]. This can occur following any exposure to a halogenated hydrocarbon. The mechanism responsible for these life-threatening irregular rhythms is thought to be a heightened sensitivity of the catecholamine receptors on heart muscle cells caused by the hydrocarbon, predisposing them to excessive catecholamine stimulation [12]. Since chloral hydrate is a halogenated hydrocarbon, a sudden onset of ventricular tachycardia or fibrillation has been described in some cases, similar to the inhalant abuse of hydrocarbons [13, 14].

As this ventricular irritability is a result of overstimulation of cardiac beta 1 receptors, the treatment to reverse and ideally prevent reoccurrence is the administration of a beta receptor antagonist. As chloral hydrate is an older medication, the agent most commonly reported in previous case reports to reverse cardiac dysrhythmias is propranolol [11, 12]. Propranolol is a long-acting beta antagonist and has the potential to complicate a resuscitation with profound and prolonged hypotension and/or bradycardia. Therefore, we recommend using the short-acting beta antagonist esmolol, which can be rapidly titrated off if needed. From our review of literature, our case would be the first documented use of esmolol for chloral hydrate-induced dysrhythmia.

Hemodialysis and charcoal hemoperfusion have been used following acute chloral hydrate poisoning [15]. This makes intuitive sense, particularly for hemodialysis based on the molecular weight of TCE of 149 Da and low plasma protein binding of 35 % [16]. These authors demonstrated that the intra-dialysis half-life did decrease to 3.2 h during hemodialysis from 12.8 h without hemodialysis. However, the patient remained comatose for more than 22 h and required repeat hemodialysis treatments. The patient in this case report did also ingest diazepam and clomipramine, which could account for prolonged decreased level of consciousness. Due to potential risks of hemodialysis in pediatric patients and unproven benefit, we opted for aggressive supportive care.

Chloral hydrate is very irritating to the gastric mucosa. Other concerning adverse effects with chloral hydrate administration include vomiting, which can lead to aspiration of stomach contents in a sedated or obtunded child. One study demonstrated an incidence of vomiting as high as 30 % in patients receiving chloral hydrate for procedural sedation [4].

Much less common but very concerning gastrointestinal adverse effects of chloral hydrate include esophagitis, gastric mucosa necrosis with subsequent perforation, and enteritis [17, 18]. This is from the potential caustic effects of chloral hydrate, particularly at large dosages. The long-term sequelae include possible esophageal stricture formation [17, 18].

Chloral hydrate is an older medication, which in our opinion should no longer be used for procedural sedation in patients of any age. Choral hydrate is associated with significant adverse effects, including death, and safer alternatives for pediatric procedural sedation should be sought and utilized. There are a number of alternative sedating agents, some oral, nasal, rectal, and parenteral and some parenteral only, e.g., midazolam, proprofol, ketamine, ketofol, with more predictable pharmacokinetics and better safety profiles [19, 20]. Regarding efficacy, there is conflicting data regarding which agent is best. Several studies have shown that midazolam is as effective if not more effective than chloral hydrate for various procedures [21, 22]. Other studies have shown chloral hydrate resulted in better sedation than other sedation medications in pediatric patients [23, 24]. However, due the potential severe adverse effects from chloral hydrate, we recommend alternative agents to chloral hydrate be used in pediatric patients.

A safe medical practice for any of these sedating medications is only providing the single dose required to perform the sedation akin to "unit dose" packaging to minimize the risk of inadvertent overdose. Verifying weight-based medications as decimal errors are not uncommon and may result in a ten-fold error. With the increasing incidence of obesity in pediatric patients knowledge of maximum doses is paramount. We discourage the practice of administering any sedation medications in a non-clinical setting e.g., home, waiting room.

We present three cases of pediatric chloral hydrate poisoning including one death all occurring in outpatient clinical settings. The practice of pre-procedure sedation should be performed only in a supervised setting where cardiorespiratory monitoring can occur in all cases.

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