IV Lipid Emulsion Infusion in the Treatment of Severe Diphenhydramine Overdose

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Patient: Female, 24
Final Diagnosis: Diphenhydramine overdose
Symptoms: Encephalopathy • hypotension • seizure
Medication: —
Clinical Procedure: None
Specialty: General and Internal Medicine

Objective: Unusual clinical course
Background: Diphenhydramine is a commonly available over-the-counter antihistamine; however, there are few documented cases of treatment when ingested in toxic quantities, where it can cause a sodium channel blockade leading to wide-complex tachycardia, seizures, and death. Conventional treatment includes sodium bicarbonate infusion, but few cases have documented the addition of lipid emulsion therapy.

Case Report: A 24-year-old African American female ingested 18 g (360 pills of 50 mg) over-the-counter diphenhydramine. She presented comatose, with hemodynamic instability and hypotension, intubated with pupil dilation to 6 to 7 mm, and initial electrocardiography findings showing a type 1 AV block with a QT/QTc of 360/402 ms which progressed into sinus tachycardia with widened QRS intervals of 134 ms and prolonged QT/QTc intervals of up to 638/759 ms. Treatment using sodium bicarbonate and magnesium was initiated; however, the intraventricular conduction delay persisted. Infusion of 20% intravenous lipid emulsion was administered; following this, the patient developed narrow complex QRS with sinus rhythm and shortened the QT/QTc interval to 448/516 ms. She recovered quickly and was transferred to inpatient psychiatric unit for further evaluation, and discharged 1 month later.

Conclusions: Lipid emulsion therapy has been utilized in treatment of various medication overdoses, but there are few documented cases in the treatment of diphenhydramine overdose. With the amount of diphenhydramine ingested by the patient in this case report, the use of combined conventional and lipid emulsion therapy was utilized in the stabilization and management of the patient, and should be considered in scenarios where conventional treatments have not improved the clinical outcome.

MeSH Keywords: Diphenhydramine • Drug Overdose • Fat Emulsions, Intravenous

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Background

Diphenhydramine is a commonly available over-the-counter antihistamine used in the treatment of allergic reactions, motion sickness, and insomnia. When ingested in toxic quantities, its anticholinergic and antihistamine properties can induce sedation, hypotension, and antimuscarinic effects in the body, which ultimately can lead to death if untreated. Treatment methods include sodium bicarbonate, hemodialysis, and supportive therapy [1].

Two previous case reports documented the successful usage of intravenous lipid emulsion infusion in the treatment of diphenhydramine overdose when the conventional methods were not successful in stabilizing the patient [2,3]. However, this case report documents the usage of intravenous lipid emulsion in a case of diphenhydramine overdose at an ingested quantity previously undocumented. With few documented usages of lipid emulsion therapy, clinicians should be aware that the option exists for severe cases. We further discuss the current literature in intravenous lipid use in cases of diphenhydramine overdose.

Case Report

A 24-year-old African American female with a previous history of depression and prior suicide attempts, ingested 18 g (360 pills of 50 mg) over-the-counter diphenhydramine as a suicide attempt and had alerted friends and family of the event. Emergency Medical Services was called by family and arrived within 1 hour; the patient was alert and oriented at time of arrival but developed tonic-clonic seizures and confusion enroute to the outside facility Emergency Medicine Department. At the Emergency Department, she presented in post ictal state. Her initial blood pressure was 70/45 mmHg. She received intravenous lorazepam 1 mg which terminated the seizures and she was started on 50 mcg/min of propofol drip. A repeat arterial blood gas (ABG) showed a pH of 7.39, pCO\textsubscript{2} of 48 kPa, pO\textsubscript{2} of 60 kPa, and HCO\textsubscript{3} of 18.5 mmol/L. Initial electrocardiogram (ECG) showed a sinus rhythm with a type 1 AV block with a QRS interval of 142 ms and QT/QTc of 536/545 ms (Figure 1). She soon developed episodes of sinus tachycardia with widened QRS and prolonged QT/QTc intervals. Poison control again was contacted. She received 4 more liters of 0.9% sodium chloride, 50 mEq of 8.4% sodium bicarbonate solution, followed by an additional 25 mEq, and 2 grams of intravenous magnesium in a 100 mL suspension over 8 hours under recommendation of poison control to prevent any further arrhythmias, which was minimally effective. No dialysis was recommended. At this point, the ICU team evaluated the patient and without a visible improvement in the patient’s QT/QTc interval and cardiac rhythm, 1.5 mL/kg

Upon arrival at the regional hospital, she was comatose, intubated with pupils nonreactive, fixed and dilated to 6 to 7 mm. Her glucose was 90 mg/dL and her vitals were blood pressure: 143/85, heart rate: 86, temperature: 36.6°C (97.8°F), weight: 60 kg. She also presented with hypoactive bowel sounds, positive Babinski’s sign, extremities were cool to palpation with no edema and skin was not flushed. Patient already had a Foley catheter from the outside hospital stay. She was placed on mechanical ventilation in the intensive care unit (ICU). The patient had 2 episodes of witnessed tonic-clonic seizures on arrival. She received intravenous lorazepam 1 mg which terminated the seizures and she was started on 0.1 mcg/kg/min and increased to 0.5 mcg/kg/min over a period of 120 minutes for her hypotension followed by another liter of normal saline. After 2 hours of resuscitation, her blood pressure was 91/47 mmHg. Urine toxicity and drug screens were negative, and serum concentrations of acetaminophen and salicylates were also negative at this time. Gastric decontamination with charcoal was started; however, after discussion with poison control, decontamination was discontinued. Instead, she received 100 mEq/mL of sodium bicarbonate 8.4% intravenously in an attempt to resolve her metabolic acidosis with a pH of 7.1 on arterial blood gas on arrival. She was then transferred to a regional hospital for further care.

Initial electrocardiogram (ECG) showed a sinus rhythm with poison control, decontamination was discontinued. With few documented usages of lipid emulsion therapy, clinicians should be aware that the option exists for severe cases. We further discuss the current literature in intravenous lipid use in cases of diphenhydramine overdose.

Figure 1. Electrocardiography taken at admission from an outside hospital showing type 1 AV block and wide QRS. The ventricular rate is 64 bpm, PR Interval of 332 ms, wide QRS interval of 142 ms, and a QT/QTc of 536/545 ms.

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of 20% intravenous lipid emulsion was administered followed by 25 mL/hr infusion as per ICU team recommendation. The patient developed narrow complex QRS with sinus rhythm, and the QT/QTc remained significantly prolonged at QT/QTC of 638/759 ms (Figure 2). This quickly shortened to 498/556 ms (Figure 3). A 25 mL/hr rate of continuous infusion over the next 24 hours was initiated. Following this, the patient maintained narrow complex QRS with sinus rhythm and shortened the QT/QTc interval to 464/532 ms (Figure 4) after 24-hour infusion. Continuous infusion was discontinued at this time as the patient was no longer hypotensive and her QT interval had improved.

After 48 hours, the patient remained in normal sinus rhythm with resolution of prolonged QT interval (Figure 5) with a QRS of 80 ms and QT/QTC of 412/444 ms and stable blood pressures.

**Figure 2.** Electrocardiography showing prolonged QT interval after resolution of wide QRS. The ventricular rate is 85 bpm, PR interval of 184 ms, QRS interval of 82 ms, and a QT/QTC of 638/759 ms.

**Figure 3.** Electrocardiography halfway through intravenous lipid emulsion. The ventricular rate is 75 bpm, PR interval of 158 ms, QRS interval of 72 ms, and a QT/QTC of 498/556 ms.

**Figure 4.** Electrocardiography after 24 hours of admission and following continuous infusion of lipid emulsion. The ventricular rate is 79 bpm, PR interval of 150 ms, QRS interval of 70 ms, and a QT/QTC of 464/532 ms.
enough to terminate mechanical ventilation and sedation. The patient was able to converse with other people in her surroundings, and could feed herself. She was transferred to the inpatient psychiatric unit for further evaluation. She continued to have lapses in her memory leading up to the suicide attempt; however, as the weeks progressed, her memory improved, and she was able to recall events and people that she had encountered during this period. There were no observed complications from the lipid emulsion therapy during her hospital and psychiatric admission. She was later discharged from the inpatient unit with follow-up appointments with an outpatient psychiatrist.

Discussion

Diphenhydramine is a first generation H1 antihistamine that acts as an inverse agonist on the H1 receptor by causing a conformational change of the receptor and stabilizing the inactive form. This leads to a reduction of mast cell and basophil released histamine effects on systemic cells by reducing the basal activity of the H1 receptor [4]. However, diphenhydramine can also bind and interact with other receptors and ion channels, such as acetylcholine receptors, serotonin receptors, and cardiac sodium channels. As such, side-effects of diphenhydramine include tachycardia, urinary retention, agitation, and hypotension. Ingested quantities exceeding 1 g of diphenhydramine can result in toxic delirium and psychosis, rhabdomyolysis, wide-complex tachycardia, seizures, and death [5]. In these scenarios, enough concentration of diphenhydramine is available to cause a sodium channel blockade, similarly to class 1A antiarrhythmic medications [4,5]. This behavior was noted in our patient with initial PR prolongation causing a type 1 AV block. Traditionally, this has been counteracted with infusion of hypertonic sodium bicarbonate, which would increase the plasma sodium ion concentration such that the sodium gradient across the affected channels would be increased [6]. Sodium bicarbonate also increases serum pH, such that there are fewer active metabolites of compounds binding to channels [7].

In this patient, conventional methods of treatment using sodium bicarbonate were initiated; however, the intraventricular conduction delay persisted. The decision to attempt a lipid emulsion therapy was made due to existing literature supporting intravenous lipid emulsion therapy in the treatment of diphenhydramine toxicity. The lipid emulsion would act as a “lipid sink” for the lipophilic diphenhydramine molecules, thereby drawing them away from sodium channels, and instead, binding to the lipid emulsion particles [8]. This would in turn resolve the sodium channel blockade and relieve the conduction delay. Lipid emulsions can also act as direct inotropes, with moderate serum triglyceride concentrations resulting in increases in blood pressure [9]. Current recommendations (ACMT 2016, AHA 2015) on intravenous lipid emulsion use for serious hemodynamic or other instability secondary to highly lipid soluble substance (off label use) is 1.5 mL/kg bolus, followed by 0.25 mL/kg/minute infusion with maximum dose of 10 mL/kg over 30 to 60 minutes [10]. Since we observed a quick response on ECG and cardiac monitor after infusion of bolus intravenous lipid emulsion and patient hemodynamically was stable, a slow infusion of intravenous lipid emulsion was utilized to help with any potential delayed release of ingested diphenhydramine. Since the maximum recommended dose of the lipid preparation used (IntraLipid®) is 500 mL within 24 hours, we infused the rest of intravenous lipid emulsion at 25 mL/hr for about 20 hours. Although the dosing used was different, but our rationale behind it was to stick with the maximum recommended safe dose of intravenous lipid emulsion. We believed this was even more important, as the dose we used was within the safe range and was much less than the infusion dose recommended by most societies.

In an animal study conducted using 24 swine, Varney et al., randomly infused swine with either sodium bicarbonate or intravenous lipid emulsion separately to counteract diphenhydramine toxicity [1]. No difference was found between the 2 methods in measured cardiac output, QRS intervals, or time to death, but results transiently favored lipid emulsion therapy.
in measured mean arterial blood pressure and systolic blood pressure [1]. In the overdose of clomipramine, a lipid-soluble tricyclic antidepressant medication which can similarly cause sodium channel blockade in overdose quantities, Harvey et al., demonstrated the use of lipid emulsion therapy in a rabbit model [11]. Rabbits were infused with either 0.9% saline solution, sodium bicarbonate, or 20% isotonic lipid emulsion and monitored for hemodynamic and ECG changes at baseline, 5-minute, and 15-minute time points. There was a 21.1 mmHg and 19.5 mmHg difference in mean arterial pressure between lipid emulsion therapy alone versus saline therapy alone at 5-minutes and 15-minutes, respectively [11]. Similarly, there was a 19.4 mmHg and 11.5 mmHg difference in mean arterial pressure between lipid emulsion therapy alone versus sodium bicarbonate therapy alone at 5-minutes and 15-minutes, respectively [11]. In the aforementioned study, they found a greater rate of change in mean arterial pressure restoration when using the lipid emulsion therapy in comparison to the other methods [11]. With contrasting results, reports of using one therapy over another may differ due to individual case limitations and methodology and therefore, don’t provide a solidified conclusion as to which therapeutic method is more appropriate in diphenhydramine overdose.

A few cases have been documented demonstrating the use of combination therapy of both the conventional treatments, such as sodium bicarbonate infusion, followed by lipid emulsion infusion. Our case closely paralleled the situation presented by the following case, yet with a much higher ingested diphenhydramine level. In the case of a patient reported by Abdi et al., the usage of lipid emulsion therapy in combination with sodium bicarbonate in the treatment of a 23-year-old male who ingested 2000 to 2500 mg of diphenhydramine was reported [2]. The patient presented with sinus tachycardia with a wide QRS of 172 ms and prolonged QTc of 577 ms [2]. Sodium bicarbonate was first used, resulting in a blood pH of 7.44; however, the ECG continued to show an intraventricular conduction delay [2]. In this case, a second infusion of sodium bicarbonate did not resolve the wide QRS, and neither did the first bolus infusion of 20% intravenous lipid emulsion. After the second bolus of lipid emulsion, the patient’s wide QRS was resolved, resulting in sinus rhythm and normal QRS width [2]. Importantly, the patient’s prolonged QTc interval was also resolved. Without treatment, prolonged QTc intervals can result in occurrences of fatal cardiac arrhythmias, such as torsades de pointes and polymorphic ventricular tachycardia.

Success in using lipid emulsion therapy has been documented in overdose scenarios with other lipophilic compounds as well. Similar to diphenhydramine’s sodium channel blockade in overdose quantities, bupropion in overdose quantities can also manifest in a sodium channel blockade. Sirianni et al., documented a case of bupropion and lamotrigine overdose resulting in altered mental status, tonic-clonic seizures, prolonged QRS-interval duration, and prolonged QTc duration. Supportive airway and fluid resuscitation methods were employed, along with the conventional therapy of an intravenous bolus of sodium bicarbonate 50 mEq; however, these were not successful as the patient transitioned into pulseless, wide complex rhythm. After administration of a 100-ml intravenous bolus of 20% lipid emulsion, a palpable pulse and sinus rhythm were restored [7].

Conclusions

With the amount of diphenhydramine ingested by the patient in our case report, the use of combined conventional therapy and lipid emulsion therapy was utilized in the stabilization and management of the patient. Other case reports have documented the use of lipid emulsion therapy in treatment of various medication overdoses; however, few have documented its application in the treatment of diphenhydramine overdose. Although conventional methodology may be effective in the treatment in the majority of overdose presentations, higher toxicity levels of compounds could potentially be more effectively managed through the combination of conventional treatment and lipid emulsion therapy. The effectiveness of intravenous lipid emulsion therapy on a patient’s hospital length of stay benefits cannot be determined as there are no comparisons made in patients with similar ingestion courses without utilizing intravenous lipid emulsion therapy. This is a limitation that should be further evaluated in future patient encounters. Intravenous lipid emulsion therapy can be considered in scenarios where conventional treatments have not improved the patient presentation.

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