Extracorporeal Cardiopulmonary Resuscitation After Diphenhydramine Ingestion

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Abstract

Introduction Diphenhydramine is a widely used first-generation histamine (H₁) antagonist that can be obtained without prescription in many countries. Massive ingestions can result in severe toxicity and even death. We describe a case of diphenhydramine overdose leading to cardiac arrest, cardiopulmonary resuscitation (CPR), and extracorporeal membrane oxygenation (ECMO) cannulation for refractory ventricular fibrillation, a process we refer to as extracorporeal cardiopulmonary resuscitation (ECPR).

Case Report Responding to a call for altered mental status, emergency medical service (EMS) personnel found an unconscious and seizing 17-year-old male. He had reportedly developed generalized tonic-clonic seizures and dysrhythmias after ingesting approximately 800 25-mg diphenhydramine tablets. He was transferred to our pediatric intensive care unit (PICU) after stabilization at a local emergency center. After approximately 7 hours of clinical stability and normalization of cardiac rhythm, electrolytes, and acidosis, he developed renewed seizure activity and accelerated ventricular rhythm leading to hemodynamic collapse and cardiac arrest. He was cannulated for veno-arterial extracorporeal membrane oxygenation (VAECMO) with CPR in progress. A pharmacobezoar located in his stomach was presumed to be the cause of his biphasic clinical deterioration. After 5 days, the patient was successfully weaned from ECMO support. Ten days later, his convalescence continued in the step-down unit and was discharged with good functional outcome.

Discussion Significant ingestion of anticholinergic substances is often fatal. This case describes a favorable outcome after ECPR and aggressive supportive management following a large intentional overdose of diphenhydramine.

Keywords Diphenhydramine · ECPR · Pharmacobezoar

Introduction

Diphenhydramine (DPH) is a first-generation H₁ antagonist in use since 1946. It is used primarily to treat allergies and as a sedative and antiemetic. Like other first-generation H₁ antagonists, DPH antagonizes central and peripheral muscarinic cholinergic receptors. Massive ingestions may be associated with significant morbidity and death.

Diphenhydramine is widely available and can be obtained without prescription in many countries. In 2016, more than 40,000 cases of isolated DPH overdoses and more than 8000 cases of DPH-combination ingestions were reported to U.S. Poison Centers. Over 20 deaths and 500 life-threatening cases were described [1].

Here, we report the case of an adolescent male who survived a massive DPH ingestion requiring extracorporeal cardiopulmonary resuscitation (ECPR) and aggressive gastrointestinal decontamination.

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Case

EMS was called for an unconscious, seizing 17-year-old male with a history of major depressive disorder who had reportedly ingested an unknown amount of 25-mg DPH tablets. His seizures stopped after 10 mg of diazepam. He was intubated in

the field without additional medications. En route to the hospital, he received 1 l of normal saline and 100 mEq of sodium bicarbonate. No dysrhythmias were noted except sinus tachycardia.

On arrival to the emergency center, his initial vital signs were as follows: blood pressure (BP) 124/63 mmHg, heart rate (HR) 108 bpm, temperature 36.7 °C, respiratory rate (RR) 16/min, oxygen saturation (SpO₂) 98%. On physical exam, pupils were fixed and dilated. He had a severe metabolic acidosis with lactic acidemia: pH 6.98, PCO₂ 69 mmHg, HCO₃[−] 16 mmol/l, base excess −16, lactate 20 mmol/l. His initial electrocardiogram (EKG) exhibited significant QTc prolongation (580 ms), and he rapidly developed an accelerated ventricular rhythm (Fig. 1). Sodium bicarbonate (300 mEq), 4 g of magnesium sulfate, 100 ml of 3% hypertonic saline, and 1 l of 0.9% normal saline were administered with subsequent pH and cardiac rhythm normalization. His lactate concentration decreased from 20 to 3 mmol/l within hours. A head CT showed no anomalies. The remaining laboratory values, including blood cell count, liver enzymes, and basic metabolic panel, were within normal limits. Urine drug screen was negative for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opioids, phencyclidine, THC, and tricyclics. Acetaminophen and salicylate levels were undetectable. Lipid rescue therapy was discussed but withheld because of his improved clinical picture. Gastrointestinal decontamination was not initiated at this time because the patient already displaying symptoms and the extent of his ingestion was not yet known. He was transferred to the pediatric intensive care unit (PICU) for further management.

Upon PICU arrival, vitals were as follows: BP 124/64 mmHg, HR 122 bpm, temperature 36.7 °C, RR 16/

min, SpO₂ 98%. Pupils were 4 mm and equally reactive. His neurologic exam was encouraging with spontaneous eye opening and purposeful extremity movement. His arterial blood gas was within normal limits, and the lactate continued to normalize. His QTc remained prolonged (500 ms) but improved from the previous EKG. An echocardiogram revealed normal biventricular systolic function. A propofol drip (20 µg/kg/min) was initiated for sedation.

Approximately 7 h after his PICU admission, the patient developed renewed tonic-clonic seizure activity associated with a combined acidosis (pH 7.11, PCO₂ 78 mmHg, HCO₃[−] 25 mmol/l, base excess −7, lactate 4.5 mmol/l). The accelerated ventricular rhythm with widened QRS recurred with subsequent hypotension (BP 60/40 mmHg) and rapid elevation in lactic acid. Two boluses of bicarbonate (100 mEq) were administered and an infusion was started. Potassium (30 mEq) and magnesium sulfate (2 g) were also given. Seizures were controlled with a midazolam infusion (2 mg/h). He required multiple doses of epinephrine (0.1 mg) for hypotension and rapid escalation of vasoconstrictor and inotropic support with vasopressin (0.05 U/min), norepinephrine (0.05 µg/kg/min), phenylephrine (0.1 µg/kg/min), and epinephrine (0.1 µg/kg/min). Initially, esmolol had been started for the dysrhythmia but was stopped because of persistent hemodynamic instability. Physostigmine (2 mg) was administered without clinical improvement, and lipid rescue therapy (1.5 ml/kg) was attempted. New clinical findings included unequally dilated and nonreactive pupils along with evidence of poor systemic perfusion.

Fig. 1 Electrocardiogram: accelerated ventricular rhythm. QTc prolongation

Because of his refractory shock, the extracorporeal membrane oxygenation (ECMO) team was consulted. Prior to cannulation, a head CT was ordered to exclude an intracranial process that would preclude ECMO. In transit to radiology, he developed ventricular fibrillation (VF) cardiac arrest and was returned to the PICU with cardiopulmonary resuscitation (CPR) in progress. Because his VF was refractory to defibrillation, he was cannulated in the femoral artery and vein during CPR, achieving adequate ECMO flows within 9 min of CPR initiation.

On day (D) 1 of ECMO (24 h post-ingestion), a pharmacobezoar was suspected on chest radiography (Fig. 2). We subsequently learned he had ingested approximately 800 pills. Endoscopy demonstrated scattered pill fragments throughout the esophageal and the gastric mucosa and a large ball of coalescing tablets in the gastric cardia (Fig. 3). Suctioning the gastric content was unsuccessful. Because of the risk of bleeding while anticoagulated on ECMO, surgical intervention was deferred. Whole-bowel irrigation (WBI) with high molecular weight polyethylene glycol was started at 1500 ml/h and was continued for 27 h, producing 18,600 ml of stool output. One hundred-gram doses of activated charcoal were also administered to adsorb the DPH. Both treatments were discontinued due to abdominal distension and concern for ileus.

The patient was progressively weaned off all pressors by D2 of ECMO (48 h post-ingestion), and he remained on a milrinone infusion for poor left ventricular function based on an echocardiogram obtained shortly after cannulation. On D4 of ECMO (96 h post-ingestion), repeat endoscopy down to the pylorus revealed no remaining pill fragments or bezoar. His cardiac function progressively recovered, he remained in sinus rhythm, and he was successfully weaned from extracorporeal support on D5 of

Fig. 2 Suspicion of pharmacobezoar

Fig. 3 Endoscopy. Large ball of coalescing tablets in the gastric cardia

ECMO. He was extubated 4 days later and transferred to an acute care floor shortly after extubation. His brain MRI showed some restricted diffusion abnormality in the posterior globus pallidus, putamen, and ventrolateral thalami concerning for hypoxic ischemic injury. He required inpatient rehabilitation for functional and cognitive deficits as well as decreased endurance and physical deconditioning. Following 8 days of intensive rehabilitation, he was discharged home with outpatient psychiatry. His functional status had recovered completely.

Discussion

There are many reports of severe DPH poisoning in children and adults [2, 3]. Signs of DPH intoxication include peripheral manifestations such as tachycardia, mydriasis, ileus, urinary retention, and anhidrosis. Central nervous system effects may present with mental status alterations ranging from coma to delirium and even seizures. In larger ingestions, DPH may cause rhabdomyolysis and dysrhythmias, including QRS widening and QT prolongation due to fast sodium channel blockade and inhibition of the repolarizing potassium channels [4, 5].

Our patient experienced an apparent biphasic intoxication. Once stabilized from severe seizures and metabolic abnormalities, he again deteriorated with recrudescence of his seizures and new onset, shock-resistant VF. Early consideration of ECMO in this patient prior to his arrest resulted in timely deployment of the resources needed to cannulate the patient. Thus, when he did arrest, his CPR duration was short and entry onto mechanical support occurred quickly.

Although the patient experienced hemodynamic collapse after receiving lipid therapy and en route to the radiology

suite, we cannot conclude a causative relationship from this intervention. The patient's arrhythmias and cardiac compromise were present prior to initiation of lipid therapy, demonstrating his need for ECMO prior to his cardiac arrest. Literature has previously suggested an inconclusive relationship between intravenous lipid therapy and DPH toxicity, although it may be detrimental in some cases [6, 7].

The administration of physostigmine, a cholinesterase inhibitor that crosses the blood-brain barrier, can reverse the central and peripheral antimuscarinic toxicity observed in significant DPH overdoses. However, in the setting of this patient's hemodynamic collapse 3 h after physostigmine administration, it is prudent to cite that its use in the setting of sodium channel blockade remains an area of debate [8].

Although in most ingestions, DPH is absorbed within hours [9], the prolonged DPH absorption from a gastric pharmacobezoar likely caused the second deterioration in our patient.

In most ingestions, patients are often symptomatic upon arrival, and gastrointestinal decontamination (GID) would be both ineffective and potentially dangerous. In massive overdoses, ileus could theoretically extend absorption time [10].

Pharmacobezoar management consists of preventing further drug absorption and eliminating the bezoar. Factors contributing to pharmacobezoar formation include host pathologies, e.g., prior surgery, gastric autonomic neuropathy, and medications that delay gastric emptying, e.g., opioids and antimuscarinic agents. Large ingestions, particularly of insoluble material as is found in controlled-release formulations, may contribute to bezoar formation [11].

Conventional radiography and endoscopy can help identify pharmacobezoars. When the composition of the bezoar is known, targeted therapies, including aggressive GID, lithotripsy, and, rarely, gastrotomy, may be employed [11–13].

When medical management fails, ECMO support has been shown to be beneficial for refractory drug-induced cardiogenic shock [2]. This case reports the successful use of ECPR for DPH-induced VF cardiac arrest.

Conclusions

Most DPH ingestions are characterized by antimuscarinic toxicity and can be treated supportively and with the specific antidote, physostigmine. Massive ingestions may be associated with seizures, rhabdomyolysis, and potentially fatal dysrhythmias. There may be an expanded role for gastrointestinal

decontamination in patients in whom a bezoar is suspected. In patients who fail to respond to aggressive medical management and develop refractory dysrhythmias and myocardial dysfunction, ECMO may be warranted as a bridge to recovery.

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Compliance with Ethical Standards

Conflict of Interest There is no conflict of interest.

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