Survival after Diphenhydramine Ingestion with Hemodialysis in a Toddler

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Abstract A 13-month-old male who ingested 20 diphenhydramine (25 mg) tablets presented with seizures and ultimately progressed to status epilepticus and wide-complex tachycardia. Due to worsening clinical course, hemodialysis was performed with temporal resolution of his symptoms. Hemodialysis may be considered in critically ill diphenhydramine overdoses not responsive to conventional supportive care.

Keywords Overdose · Status epilepticus · Wide-complex tachycardia

Introduction

Antihistamine exposures account for 3.5% of pediatric (≤ 5 years old) cases reported to the National Poison Data System (NPDS) [1]. The majority of accidental or intentional ingestions involve sedation or antimuscarinic symptoms. In massive overdose, lethal tachydysrhythmias and status epilepticus have rarely been described [2, 3]. Hemodialysis has been considered ineffective in cases of diphenhydramine toxicity based on its physical properties and kinetics at therapeutic doses [4]. We report a case of diphenhydramine ingestion in a toddler in which hemodi-

alysis was performed for both wide-complex tachycardia and persistent seizures.

Case Report

A 13-month-old (10-kg) male presented to the emergency department (ED) after he was found playing with an empty bottle of Unisom® gelcaps (diphenhydramine 25 mg). His mother determined that 20 gelcaps were missing (1,000 mg; 50 mg/kg). Prior to emergency medical services (EMS) transport to the ED, the child had experienced a self-limiting seizure at home. During EMS transport, he had three additional seizures, each of which was terminated by an intramuscular injection of 1 mg of midazolam. He arrived in the ED within 45 min of being found with the bottle.

ED Course

On arrival, his temperature was 37.6°C (99.6°F), his blood pressure was 99/56 mm Hg, his heart rate was 188 beats/min, his respiratory rate was 30 breaths/min, and his oxygen saturation on 100% blow-by oxygen was 100%. Physical exam revealed a somnolent child with decreased responsiveness but who would withdraw to pain, moving all extremities equally. Pupils were 4 mm and minimally reactive to light. Cardiac auscultation was significant for tachycardia without murmurs or gallops. Bowel sounds were diminished. The skin was hot and dry. The remainder of the exam was within normal limits. His past medical history was significant for a febrile seizure 3 months earlier. He had no current illnesses and was taking no medications. Within several minutes after arrival, the child had another generalized

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Fig. 1 Initial ECG

tonic–clonic seizure, this time with left gaze deviation. A tibial interosseous line was established to administer 1 mg of lorazepam and 1 mg of midazolam that terminated the seizure. An IV was then inserted, and he was given a 20-mL/kg bolus of normal saline.

The child's ECG in the ED 1 h after ingestion showed sinus tachycardia with a rate of 188 bpm, a QRS duration of 68 ms, a QTc of 407 ms, and no injury pattern (Fig. 1). Laboratory results from the ED revealed WBC 15,800, hematocrit 36.1%, platelets 551,000, sodium 140 mmol/L, potassium 4.3 mmol/L, chloride 105 mmol/L, CO₂ 29 mmol/L, blood urea nitrogen 16 mg/dL (5.7 mmol/L), creatinine 0.3 mg/dL (26.5 μmol/L), salicylate <4 mg/dL, acetaminophen <10 μg/mL, and INR 0.96. A urine immunoassay detected benzodiazepines as well as the presence of an organic base, later confirmed as diphenhydramine. The remainder of the child's stay in the ED was uneventful, and

he was admitted to the pediatric ICU (PICU) for further observation.

PICU Course

Approximately 3.5 h after ingestion, the child's telemetry monitor showed an intermittent atrial flutter with a widened QRS of 120 ms (Fig. 2) and he began to having increasing tonic–clonic seizure activity, with little response from lorazepam 1 mg IV and midazolam 5 mg IV, this activity ultimately progressed to status epilepticus. He was intubated and given a loading dose of 20 mg/kg of IV fosphenytoin. He was treated with multiple (1 meq/kg) boluses of sodium bicarbonate for his widened QRS; however, the atrial flutter with widened QRS continued intermittently after being placed on a sodium bicarbonate infusion. Dopamine (5 μg kg⁻¹ min⁻¹) was started for

Fig. 2 Rhythm strip

hypotension (the blood pressure at this time was 54/29 mm Hg). An echocardiogram revealed global hypokinesis without focal deficit.

Approximately 11 h after ingestion, the child remained hypotensive, tachycardic, and hyperthermic with a BP of 65/28, pulse 122, and temperature 38.6°C, with persistent seizures. At this time, due to his deterioration despite treatment, nephrology was consulted due to our experience with hemodialysis in an adult diphenhydramine overdose [4], and after discussion between the PICU team, toxicology, and nephrology, it was felt that dialysis was a reasonable therapeutic option. Epinephrine ($0.03 \mu\text{g kg}^{-1} \text{min}^{-1}$) as well as upward titration of dopamine was used in attempt to compensate for continued hypotension (66/31 mmHg) during his dialysis. Forty-five min into his first 4-h dialysis treatment, the patient's diphenhydramine concentration was 3,900 ng/mL (therapeutic range 100–1,000 ng/mL). He had no seizure activity or QRS widening following his first dialysis treatment, though he did have an ongoing sinus tachycardia in the 100–120 bpm range. Twenty-six hours after his ingestion, he remained in a narrow-complex tachycardia with a heart rate averaging 120 bpm and with a systolic blood pressure between 80 and 100 mm Hg. At the discretion of the nephrologist, a second dialysis treatment was begun and lasted 3 h.

After the second dialysis treatment, the child remained stable and was weaned off sedation and pressor drips, and he was extubated on hospital day 2. He was then transferred to the ward on hospital day 3 and discharged home neurologically intact without further sequelae on hospital day 4.

Discussion

Diphenhydramine has rapid absorption, with peak blood and tissue concentrations 2 h after ingestion of oral tablets [5]. In the case presented, the ingestion of liquid gelcaps had onset of symptoms within 30 min. The half-life in children has been estimated to be 5.4 ± 1.8 h [5] and may be prolonged in overdose. Severe symptoms, including coma, seizures, and dysrhythmias, appear to be more likely with ingestions over 1.0 to 1.5 g in adults or approximately 15–20 mg/kg in children [6].

While serum concentrations do not directly correlate with toxicity [7], fatal diphenhydramine blood concentrations in pediatric ingestions have ranged from 69 to 12,100 ng/mL [8] (therapeutic range 100–1,000 ng/mL). The concentration of 3,900 ng/mL reported in our case was obtained 11.75 h after ingestion (and after 45 min of dialysis); this value is well within the range of concentrations at which fatalities have been reported.

Published pharmacokinetics suggesting that diphenhydramine would not be amenable to removal by hemodialysis include high lipophilicity, a large volume of distribution (3–4 L/kg), a high degree (98%) of protein binding, and two-compartment kinetics with rapid clearance from serum to tissue [4]; however, several previous publications have reported survival and improvement in clinical course with hemoperfusion and hemodialysis in adults [4, 9, 10]. The volume of distribution, protein binding, and kinetics of diphenhydramine in overdose are poorly described, and it is unclear whether these may make diphenhydramine more amenable to hemodialysis than previously predicted. While clearance rates have not been reported for hemodialysis, in *in vitro* experiments with plasma diphenhydramine concentrations of at least 10 $\mu\text{g/mL}$, hemoperfusion removed 96–99% of diphenhydramine from plasma [7]. Exchange transfusion has also been used successfully in a 15-month-old toddler who presented with seizures after confirmed diphenhydramine ingestion [11]; however, this modality is not as readily available as hemodialysis.

Conclusion

This is the first case report we are aware of that describes the use of hemodialysis for diphenhydramine overdose in a child. The patient's widened QRS, tachycardia, and seizures temporally resolved with hemodialysis, suggesting that further study of hemodialysis in diphenhydramine toxicity is warranted and that hemodialysis may be considered in critically ill diphenhydramine overdoses that do not respond to conventional supportive care.

Conflict of interest The authors report no conflicts of interest.

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