

Generalized tonic clonic seizure as the primary manifestation of diphenhydramine overdose

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Abstract

Purpose: A case of generalized tonic clonic seizure development due to intentional diphenhydramine ingestion is described.

Summary: A 19-year-old Caucasian woman with a past medical history notable for post-traumatic stress disorder, depression and previous suicide attempt was brought to our tertiary academic medical center after experiencing a witnessed seizure. Upon questioning the patient, who was tachycardic, intermittently agitated and unresponsive, reported ingestion of 600 mg of diphenhydramine approximately one hour prior. While in the emergency department the patient experienced a second, witnessed, generalized tonic clonic seizure that resolved spontaneously. An electrocardiogram revealed sinus tachycardia with normal corrected Q-T interval (QTc), and an electroencephalogram did not reveal any evidence of underlying epilepsy. Reported serum and urine toxicologic screening were negative for other drugs of abuse. The patient was hydrated with intravenous normal saline and received intensive care monitoring for 24 hours before being transferred to the medical floor. The Naranjo Adverse Drug Reaction Probability Scale indicated a probable relationship (score of 6) between diphenhydramine overdose and development of the generalized tonic clonic seizure in this patient.

Conclusion: Previously, seizure development with or without concomitant cardiac manifestations, have only been reported in the adolescent or adult literature after ingestion of greater than 1 gram of diphenhydramine. This case report indicates that in adult patients, heightened monitoring for the development of seizures, among other toxicities, should be considered for all patients receiving management secondary to diphenhydramine overdose, regardless of the reported ingested dose.

Keywords

diphenhydramine; overdose; seizure; toxicology

Introduction

Diphenhydramine is an over-the-counter antihistamine that is widely used in the management of allergic reactions and/or allergy symptoms. The major actions of diphenhydramine arise from its inverse agonism on peripheral Histamine 1 (H₁) receptors and antagonism of central H₁ receptors. However, diphenhydramine also exerts anticholinergic and sodium channel blocking properties, which contribute to its anti-Parkinsonism and local anesthetic effects, respectively [1]. Diphenhydramine is available in

individual oral and intravenous (IV) forms and can be found in many combination medication products. The oral dosage forms are up to 60% bioavailable and produce maximal effects within three hours [2]. Due to ease of availability, low cost, and sedative effects diphenhydramine ingestion is one of the most common causes of drug toxicity and overdose. In 2014 the American Association of Poison Control Centers reported that diphenhydramine was the second-most frequent pharmacologic agent associated with overdose fatality in patients aged 13-19 years [3]. Previous literature has identified that, in adolescent and adult patients, serious adverse effects including the development of seizures and cardiac toxicities are associated with ingestion of \geq one gram of diphenhydramine [4-11]. Here we report the development of tonic clonic seizures with reversible cardiac toxicity in a patient having ingested 600 mg of diphenhydramine.

Case Presentation

A 19 year-old Caucasian woman (height, 160 cm, weight, 60.3 kg) was brought via emergency medical services to the emergency department (ED) at a tertiary academic medical center after experiencing a witnessed, new-onset seizure. Upon questioning, it was found that the patient had ingested 24 tablets of diphenhydramine (600 mg, 9.95 mg/kg) approximately 1 hour prior to the development of her first seizure. The patient's past medical history was significant for post-traumatic stress disorder, anxiety, major depressive disorder and previous suicidal attempt but negative for a history of seizure disorder. At the time of admission the patient's home medications included aripiprazole 5 mg at 12 PM and 15 mg at bedtime orally/day, citalopram 20 mg orally/day, clonidine 0.1 mg every morning and every evening orally/day and trazodone 50 mg orally/day as needed for insomnia.

Upon presentation to the ED, the patient was lethargic with intermittent episodes of agitation and non-responsiveness. The patient's respiratory and cardiac physical examination was negative for cough, chest tightness or pain, shortness of breath, wheezing, stridor and palpitations. She was noted to be tachycardic, heart rate of 173 beats/minute, a QTc duration of 470 milliseconds, measured blood pressure of 105/69 mmHg, respiratory rate of 20 breaths/minute with an oxygen saturation of 99% on room air and a recorded oral temperature of 37°C. Additional, pertinent, laboratory data from admission include a carbon dioxide level of 11 mmol/L, anion gap of 24 mmol/L, serum creatinine of 1 mg/dL, and a blood glucose of 100 mg/dL. An initial arterial blood gas demonstrated an anion-gap metabolic acidosis (pH: 7.07, pCO₂: 31, pO₂: 125 mmHg and HCO₃: 9 mmol/L) and the lactic acid level was > 17 mmol/L. All other serum electrolytes and blood counts were within institutional normal limits. Serum and urine toxicology screening performed in the ED was notable only for the presence of benzodiazepines, which was attributed to the use of lorazepam prior to hospitalization in the management of her seizure by emergency medical technicians. Intravenous (IV) normal saline was initiated at a rate of 2000 mL/hour x 2 hours and a repeat arterial blood gas demonstrated a corrected metabolic acidosis (pH: 7.38, pCO₂: 38, pO₂: 46 mmHg and HCO₃: 22 mmol/L).

During her initial assessment, the patient developed a second, witnessed, tonic clonic seizure. During this episode a repeat electrocardiogram (ECG) showed sinus tachycardia with normal QT_c duration (heart rate of 111 beats/minute and a QTc of 442 milliseconds). An electroencephalogram (EEG) did not demonstrate any underlying epileptic changes during this episode. No further neurologic imaging was undertaken during this admission. The regional Center for Poison Control was contacted, and

recommended to maintain IV hydration and provide close hemodynamic monitoring but recommended against the use of physostigmine, or any other interventional agent(s), until adequate fluid resuscitation had been completed. No further neuroleptic pharmacologic agents were used during the patients admission based on recommendations from the Department of Neurology.

Ultimately, the patient was intubated for airway protection due to sustained non-responsiveness and an inability to follow commands and was admitted to the medical intensive care unit (MICU) for close monitoring. Once in the MICU the patient received one-time IV doses of midazolam 4 mg and succinylcholine 50 mg along with IV lactated ringer (rate: 75 ml/hour) and IV propofol (rate: 5 mcg/kg/min) infusions. The patient remained neurologically and hemodynamically stable and 24 hours later was extubated and transferred to the medical ward. On hospital day two a repeat electroencephalogram (EEG) was performed which revealed mild diffuse slowing, attributed to drug-induced encephalopathy, with no evidence of epileptiform discharges. At that time all prior to admission medications were restarted and the patient was recommended for placement within an inpatient psychiatric hospital by the Department of Psychiatry due to her multiple, recent, suicidal attempts. The use of the Naranjo Adverse Drug Reaction Probability Scale indicated a probable relationship (score of 6) between diphenhydramine overdose and generalized tonic clonic seizure [12].

Discussion

Diphenhydramine, due to its widespread availability, is a very common agent that can lead to the development of severe morbidity, and mortality, during intentional or unintentional overdose [1-11]. Given diphenhydramine's effects on blocking fast sodium channels, which gives rise to QRS prolongation, this may result in the development of wide complex tachycardia, myocardial depression and sudden death [1-2]. Furthermore, the histamine receptor agonism of diphenhydramine is thought to mediate an anticonvulsant effect, and blockade of these receptors likely causes higher rates of epileptogenic activity, leading to the development of generalized tonic clonic or myoclonic seizures [5-6].

One of the most challenging questions to address in the field of clinical toxicology is accurately predicting the maximum quantity of a drug product that can be safely ingested before the development of severe adverse effects are seen. Currently, few studies have evaluated the dose-response profile of diphenhydramine. In one study, Radovanovic and colleagues classified the symptoms of diphenhydramine toxicity, ranging from mild (development of somnolence, nausea/vomiting, tachycardia and other anticholinergic signs), to moderate (development of agitation, hallucination and ECG changes) and severe symptoms (development of seizure and coma) [7]. This study demonstrated a dose dependent toxicity, and the authors concluded that ingestion of diphenhydramine in doses higher than one gram was associated with the development of severe symptoms requiring patient hospitalization and monitoring. In a separate study on diphenhydramine overdose in children, Stojanovski and colleagues analyzed 2 years of data from U.S. poison centers and did not find a dose-response relationship [8]. However, both of these studies relied on patient-reported estimates of the ingested quantity of diphenhydramine without any laboratory confirmation, and did not categorize toxicities based on a milligram per kilogram basis. To better address the conflicting data, Benson and colleagues reviewed available data in children and adults who ingested acetaminophen and diphenhydramine, as a fixed combination, and used serum acetaminophen concentrations as a surrogate

marker for the ingested dose of diphenhydramine [9]. Based on these findings, the authors reported that diphenhydramine produces a dose dependent toxicity with mild signs of intoxication occurring at a weight-based dose of 6-7 mg/kg, with more severe symptoms occurring at a dose of ≥ 8.2 mg/kg. Additionally, Zareba and colleagues found that patients who developed seizures ingested an average dose of diphenhydramine three times higher doses than that of those who did not develop seizures [11]. Furthermore, these patients also developed a significantly longer QT_c duration than patients who did not experience seizure development [11].

To our knowledge, this is the first case report of generalized tonic clonic seizure secondary to diphenhydramine overdose in the absence of cardiac conduction abnormalities. It is also important to note that the development of seizure activity was seen in this patient at a comparatively lower weight-based dose of diphenhydramine compared to other previously published case reports. One possible explanation of this anomaly could be the co-ingestion of other substances that may lower the seizure threshold, such as trazodone and citalopram, in conjunction with diphenhydramine. However, the literature implicating these two agents in the development of new onset-seizures is scant. Additionally, the patients serum and urine toxicology, which was negative, add further supporting evidence that the development of new-onset seizure is likely attributed to the diphenhydramine. Furthermore, the use of the Naranjo Adverse Drug Reaction Probability Scale score leads additional credence to this attribution. Lastly, the patient also underwent EEG monitoring, which did not reveal any structural lesion or focal nidus of epilepsy, suggestive of drug overdose as the most likely etiology of her seizure development.

Conclusion

This case report adds additional, and new, evidence that diphenhydramine ingestion in doses less than one gram can be associated with generalized tonic clonic seizure development in the absence of any other signs of severe toxicity or QT_c prolongation, and reinforces the need to evaluate ingestion of diphenhydramine on a milligram per kilogram basis. Furthermore, this case highlights the continual need for monitoring of all toxicological events that may occur in patients after ingestion substances, including diphenhydramine, by pharmacists, nursing staff and medical providers, regardless of the ingested quantity.

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