CASE REPORT

QT interval prolongation and rhabdomyolysis associated with diphenhydramine toxicity: a case report

Zain Ali a, Mariya Khan b, Waqas Ullah a, Atsoufui A. Kpehor a and Muhammad Arslan Cheema a

aInternal Medicine, Abington Memorial Hospital, Abington, PA, USA; bCivil Hospital, Dow University of Health Sciences, Karachi, Pakistan

ABSTRACT
Diphenhydramine is a widely available, over-the-counter medication used for allergies and as a sleeping aid. When used in prescription doses, it is generally safe. Overdose of the medication has been associated with dangerous and life-threatening outcomes. Our case describes diphenhydramine toxicity manifesting with two rare but potentially life-threatening complications, rhabdomyolysis, and QT prolongation. Laboratory testing for diphenhydramine levels are not widely available. We recommend a high degree of suspicion for these complications when evaluating patients with diphenhydramine overdose, to adequately manage and prevent untoward outcomes.

1. Introduction
Diphenhydramine is a commonly used and widely available over the counter antihistaminic drug, used for allergic reactions as a compound in cold medicines, and as a sleeping aid [1,2]. Pharmacologically, this is a first-generation H1 Antihistaminic agent belonging to the ethanalamine subclass. Its anti-inflammatory and anti-allergic actions are mediated by blocking off mast cell and basophil derived histamine on target tissues while the sedative effect is thought to be related to its anticholinergic action [3]. Diphenhydramine overdose commonly manifests as anticholinergic toxicity; However, high doses of diphenhydramine ingestion have been associated with interventricular conduction delay [4]. A less reported manifestation of diphenhydramine overdose is rhabdomyolysis [5]. Here we report a case of diphenhydramine overdose, manifesting with both of these rare side effects.

2. Case presentation
A 53-year-old female with a history of prior psychiatric hospitalization for suicidal ideation was brought to the emergency department, after being found confused, and wandering in a field. She was found to have two bags of diphenhydramine with her. The patient was not a reliable historian and on questioning initially admitted to taking the pills in an attempt to sleep.

On presentation to the emergency department, she was agitated and confused. On arrival, she was registered to have a temperature of 100.1 F, blood pressure of 188/111 mmHg, pulse rate of 129 beats/min, and a respiratory rate of 20/min with oxygen saturation of 96% on room air.

On initial physical examination the patient appeared flushed, pupils had mydriasis, bilaterally dilated up to approximately 9 millimeters, and was non-reactive to light. Mucous membranes were dry, lungs were clear to auscultation. An abdominal examination revealed sluggish bowel sounds, neurological examination was not suggestive of focal neurological deficits. No evidence of trauma was identified. Signs, symptoms and physical examination on presentation, were consistent with anticholinergic toxicity.

Initial laboratory studies showed her to have WBC of 19.5 (RI 4.0–12.0 K/UL) with predominant neutrophils, hemoglobin 14.8 (RI 12.0–16.0 G/DL), BUN was 11 (RI 0–23 MG/DL), creatinine was 0.88 (RI 0.00–1.11 MG/DL) sodium was 139 (RI 135–145 MEQ/L), potassium was 2.7 (RI 3.5–5.1 MEQ/L), AST 123 (RI 5–34 U/L), ALT 40 (RI 0–55 U/L), bicarbonate 19 (RI 20–31 MEQ/L), magnesium 2.5 (RI 1.6–2.6 MG/DL), calcium 10.3 (RI 8.4–10.2 MG/DL), albumin 4.8 (RI 3.3–4.7 MG/DL), phosphorus 1.4 (RI 2.3–4.7 MG/DL), TSH 1.058 (RI 0.350–5.50 UIU/ML). Cardiac troponin was found to be elevated at 0.32 (RI <0.10 ng/ml). Investigations that followed included urine toxicology, which was negative for Amphetamine, Benzodiazepine, Barbiturate, Cocaine, Opiates, Phencyclidine, Methadone, Propoxyphene, and Cannabinoids. Urinalysis revealed her to have hematuria, proteinuria of 100 MG/DL, and as a sleeping aid. When used in prescription doses, it is generally safe.

KEYWORDS
Diphenhydramine toxicity; anticholinergic toxicity; rhabdomyolysis; QTc prolongation

CONTACT Zain Ali zainali.8686@gmail.com Internal Medicine, Abington Memorial Hospital, 1200 Old York Rd, Abington, PA 19001, USA © 2020 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group on behalf of Greater Baltimore Medical Center. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Arterial blood gas on initial presentation showed pH 7.37, PaCO2 37.9, HCO3 21.7, Lactate 3.61, PO2 32.4. An Electrocardiogram obtained on presentation showed shows sinus rhythm at a rate of 99 beats/min with a QTC interval of 487 ms. Aggressive hydration with 0.9% normal saline was initiated. Over the next few hours, serial electrocardiograms showed development of a right bundle block with significant QTC interval prolongation, of 765 ms.

The patient was transferred to the Intensive care unit to monitor for deterioration. Given the patient’s prolonged QTC interval and the rhabdomyolysis, sodium bicarbonate infusion was initiated. Transthoracic echocardiogram was done suggesting a normal left ventricular function, with no structural or wall motion abnormalities. Decremental QTC intervals were seen on serial electrocardiograms.

There was an improvement in her mental status and stabilization of vital signs with supportive care and hydration. Creatinine kinase levels (CK), however continued to rise and peaked at 32,343 (29–168 U/L) by day 2 of her hospitalization. Thereafter, a declining trend in serum creatine kinase levels was seen with aggressive hydration. No renal compromise was observed. Serum creatine kinase at discharge was 211 U/L.

The patient was evaluated by psychiatry. She confessed to having overdosed on the medication to harm herself, she was started on antidepressant medications and was admitted to inpatient psychiatric facility for suicidal ideation.

3. Discussion

Diphenhydramine is an inverse histamine receptor antagonist, which binds to the H1 receptor to decrease the level of receptor’s basal activity. It acts as competitive antagonists at muscarinic acetylcholine receptors and as antagonists at serotonin receptors [3].

Diphenhydramine may cross the blood-brain barrier and cause anticholinergic symptoms including delusions, psychosis, agitation, and rarely seizures. Peripheral effects of the anticholinergic toxidrome manifest as mydriasis, cutaneous vasodilation, hyperthermia, tachycardia, anhidrosis, gastrointestinal dysmotility, and urinary retention. Our patient’s initial presentation was consistent with anticholinergic toxicity associated with the diphenhydramine overdose. Overdose may manifest as prolonged QTC with wide complex tachycardia [4], and significant rhabdomyolysis, but these adverse effects occurring concurrently have rarely been reported in the literature.

The arrhythmogenicity of antihistamines at supratherapeutic doses may be related to parasympathetic blockade and its effect on potassium channels [6], and sodium channels similar to Class 1 antiarrhythmics [3].

A retrospective study evaluated the electrocardiographic abnormalities in 126 patients with diphenhydramine overdose. The majority of cases reported greater-than 500 mg of DPH ingestion, with significant prolongation corrected QT intervals when compared to the control population. No cases of Torsades de Pointes were noted in the study, with DPH related tachycardia and reverse use dependence of ionic channels proposed to have prohibited QTc prolongation progressing to torsades [6]. Pratt et al, however in their observational cohort evaluation did report two cases of Torsades de Pointes associated with diphenhydramine use [7]. Husain et al also described QTc prolongation and non-sustained polymorphic tachycardia in a patient overdosing on diphenhydramine [8]. Other electrocardiographic manifestations reported in the literature include the right bundle branch block and QTc prolongation similar to seen in our case and atroventricular blockade [9].

A rare side effect of diphenhydramine overdose is rhabdomyolysis. The exact mechanism of rhabdomyolysis remains unclear. However, it has been postulated that antihistamine may cause direct injury to the muscle. Damage to the sarcolemma may lead to extravasation of intracellular contents, and thus increasing sodium into the cell. High intracellular sodium levels activate the energy-dependent sodium/potassium ATPase, depleting ATM and contributing to cell injury. Another mechanism proposed, is the increase in intracellular sodium, which leads to an increase in intracellular calcium, thus activating proteolytic enzymes and cell injury [10].

Our patients CK levels peaked at 32,343 U/L (29–168 U/L), which to our knowledge this is the highest CK levels reported in literature associated with diphenhydramine induced rhabdomyolysis. Compounding factors that may potentiate rhabdomyolysis in cases of toxicity include seizures, hypoxia, immobilization, and compartment syndrome. However, in our case and other reported literature, these factors did not seem to be implicated [5].

Acute kidney injury is a potential complication of rhabdomyolysis. Aggressive repletion of fluids has been established as the main intervention to prevent kidney injury in rhabdomyolysis, the composition of the fluid used, and the rate of administration remains debatable. A study comparing Ringer’s lactate with normal saline in rhabdomyolysis associated with another first-generation antihistamine, doxylamine demonstrated no difference in time interval to the normalization of CK levels [11].

The recommended therapy for anticholinergic toxidrome is mainly supportive. Benzodiazepines can be used to treat agitation and seizures. Phystostigmine may be utilized in patients manifesting peripheral and central anticholinergic toxicity [12]. Dexmedetomidine has also been reported to be utilized in addition to...
benzodiazepines for agitation [13]. Interestingly Donepezil, a centrally acting acetylcholinesterase inhibitor has also been used with success to manage symptoms of diphenhydramine overdose in the unavailability of physostigmine [14].

As in our case, hypertonic sodium bicarbonate infusion has been used to counter cardiotoxicity in DPH overdose. The mechanism seems to be based on increasing the plasma sodium ion concentration via increasing the sodium gradient across the affected channels. Also, sodium bicarbonate increases the serum pH, and may reduce active metabolites binding to channels.

A novel approach is use of intravenous lipid emulsion therapy in patients with diphenhydramine poisoning, not responding to sodium bicarbonate. The lipid emulsion acts as a ‘lipid sink’ for the lipophilic diphenhydramine molecules, reducing sodium channel blockade and relieving the conduction delay [15,16]. Our patient received bicarbonate infusion with decremental QTC intervals. Vigorous hydration was employed, and despite the massive rhabdomyolysis, she did not develop renal compromise.

4. Conclusion

Our case highlights two uncommon, concomitant complications of diphenhydramine toxicity. DPH continues to be commonly used, easily available over the counter medication. Overdose has the potential to cause harm with deadly outcomes. New antihistamines with a better side effect profile be used. Laboratory testing for serum diphenhydramine levels are not widely commercially available. We recommend a high level of suspicion in cases of overdose, monitoring for arrhythmias and rhabdomyolysis, two potentially life-threatening complications.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Zain Ali http://orcid.org/0000-0002-5457-9420
Waqs Ullah http://orcid.org/0000-0002-4850-0309
Muhammad Arslan Cheema http://orcid.org/0000-0002-9161-722X

References

[1] Simonsen LP. What are pharmacists dispensing most often. Pharm Times. 1991 Apr;3:57–71.
[2] Rickels K, Morris RJ, Newman H, Rosenfeld H, Schiller H, Weinstock R. Diphenhydramine in insomniac family practice patients: a double-blind study. J Clin Pharmacol. 1983 May 6;23(5-6):234–242.
[3] Vearrier D, Curtis JA. Case files of the medical toxicology fellowship at Drexel University. J Med Toxicol. 2011 Sep 1;7(3):213–219.
[4] Abdi A, Rose E, Levine M. Diphenhydramine overdose with intraventricular conduction delay treated with hypertonic sodium bicarbonate and iv lipid emulsion. West J Emerg Med. 2014 Nov;15(7):855.
[5] Emadian SM, Carvati EM, Herr RD. Rhabdomyolysis: a rare adverse effect of diphenhydramine overdose. Am J Emerg Med. 1996 Oct 1;14(6):574–576.
[6] Moss AJ, Rosero SZ, Hajj-Ali R, Konecki J. Electrocardiographic findings in patients with diphenhydramine overdose. Am J Cardiol. 1997 Nov 1;80(9):1168–1173.
[7] Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louw W, Moyé L. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. Am J Cardiol. 1994 Feb 15;73(5):346–352.
[8] Husain Z, Hussain K, Nair R, Steinman R. Diphenhydramine induced QT prolongation and torsade de points: an uncommon effect of a common drug. Cardiol J. 2010;17(5):509–511.
[9] Thakur AC, Aslam AK, Aslam AE, Vasavada BC, Sacchi TJ, Khan IA. QT interval prolongation in diphenhydramine toxicity. Int J Cardiol. 2005 Feb 15;98(2):341–343.
[10] Khosla U, Ruel KS, Hunt DP. Antihistamine-induced rhabdomyolysis. South Med J. 2003 Oct 1;96(10):1023–1027.
[11] Cho YS, Lim H, Kim SH. Comparison of lactated Ringer’s solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. Emergency Med J. 2007 Apr 1;24(4):276–280.
[12] Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med. 2000 Apr 1;35(4):374–381.
[13] Walker A, Delle Donne A, Douglas E, Spicer K, Pluim T. Novel use of dexmedetomidine for the treatment of anticholinergic toxidrome. J Med Toxicol. 2014 Dec;10(4):406–410.
[14] Ahmad J, Hasan MJ, Anam AM, Barua DK. Donepezil: an unusual therapy for acute diphenhydramine overdose. BMJ Case Rep CP. 2019 Mar 1;12(3):e226836.
[15] Cherukuri SV, Purvis AW, Tosto ST, Velayati A. IV lipid emulsion infusion in the treatment of severe diphenhydramine overdose. Am J Case Rep. 2019;20:758.
[16] Yu JH, Chen DY, Chen HY, Lee KH. Intravenous lipid-emulsion therapy in a patient with cardiac arrest after overdose of diphenhydramine. J Formos Med Assoc. 2016 Nov 1;115:1017–1018.