Case Report

Cardiac arrest caused by diphenhydramine overdose

Tomoya Nishino, Shinjirou Wakai, Hiromichi Aoki, and Sadaki Inokuchi

Department of Emergency and Critical Care Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan

Case: A 45-year-old man presented to our emergency department with disturbance of consciousness; he had mentioned to his family earlier about a drug overdose. When first responders arrived, he suffered cardiac arrest. Cardiac arrest due to drug overdose was diagnosed.The patient was supported with venoarterial extracorporeal membrane oxygenation. Arterial blood gas showed mixed acidosis, and electrocardiogram showed junctional rhythm and complete right bundle branch block.

Outcome: The patient's blood pressure gradually decreased, and he died on the third day of hospitalization. After death, his serum diphenhydramine concentration at the time of arrival was found to be 18.7 μg/mL.

Conclusion: Although diphenhydramine is regarded as a safe medication, it shows dose-dependent toxicity. High intake is associated with death; therefore, caution should be exercised in cases of drug overdose. Developing a procedure for rapid measurement in the emergency department should be a priority.

Key words: Cardiotoxicity, H1 histamine receptor antagonist, liposoluble, over-the-counter drug, venoarterial extracorporeal membrane oxygenation

BACKGROUND

DIPHENHYDRAMINE (DPH), A first generation H1 histamine receptor antagonist, is widely used as an over-the-counter (OTC) drug; therefore, the frequency of its overdose is high. However, cardiac arrest due to overdose is rare because of its wide therapeutic range. Here, we report the case of a 45-year-old man who suffered cardiac arrest and died despite receiving intense venoarterial extracorporeal membrane oxygenation (VA-ECMO).

CASE

A 45-year-old man with no significant medical history or any reported regular medication was transferred to our emergency department in February because of disturbance of consciousness. From the history reported by family members, he had returned home 16 h before being admitted to the hospital and informed his family that he had consumed an overdose of an OTC drug. The details about the drug and its amount could not be known because the patient did not remember the amount ingested and the medication container could not be found. The patient had ingested the drug outside the home then went swimming in the ocean. At 14 h before admission, his family reported that he went to bed and was checked by his parents every hour. Although he was able to speak until 1 h before admission, he was groaning and feeling disturbed. His parents called for an ambulance; however, he suffered cardiac arrest when the ambulance arrived. A helicopter was requested, and evaluation by the ambulance crew revealed pulseless electrical activity. Cardiopulmonary resuscitation (CPR) was initiated, and continued assessment by the doctor and helicopter crew revealed asystole. After the patient received an i.v. line, intubation, continuous CPR, and 2 mg adrenaline by the doctor and helicopter crew, spontaneous circulation returned. They also administered 0.5 mg atropine because his heart rate was approximately 40 beats/min. Initial evaluation at the emergency department revealed a Glasgow Coma Scale (GCS) of E1V1M1, systolic blood pressure of approximately 60 mmHg (only carotid artery was palpable), heart rate of 100 beats/min, axillary temperature of 36.7°C, oxygen saturation (SpO_2) of 83% (O_2,

Corresponding: Tomoya Nishino, MD, Department of Emergency and Critical Care Medicine, Tokai University School of Medicine, Simokasuya143, Isehara, Kanagawa 259-1193, Japan. E-mail: i10ve69@yahoo.co.jp.

Received 12 Jan, 2018; accepted 24 May, 2018; online publication 25 Jun, 2018

Funding Information

No funding information provided.

10 L/min), and 6-mm dilation of both pupils without reflex. No injury marks were found. Cardiac arrest due to drug overdose was diagnosed, and VA-ECMO was initiated 20 min after arrival.

Laboratory tests revealed mixed acidosis, liver and renal dysfunction, elevated creatine kinase levels, and the Triage Panel for Drugs of Abuse (SYSMEX Corporation, Kobe, Japan) was negative (Table 1).

Non-contrast computed tomography (CT) of the head showed loss of gray–white matter differentiation without hemorrhage, and contrast-enhanced CT of the trunk showed no pulmonary embolism, aortic dissection, or free air. Electrocardiography revealed junctional rhythm, but QTc could not be evaluated because of complete right bundle branch block (Fig. 1). Bedside transthoracic echocardiography showed good wall motion with no asynergy, pericardial effusion, left ventricular hypertrophy, or right ventricular overload.

The patient was treated with VA-ECMO, given 0.4 μg/kg/min adrenaline, and underwent gastric lavage. His potassium level elevated to 7.2 mEq/L; thus, he was treated with insulin and glucose. Despite treatment, his blood pressure gradually decreased. Bedside transthoracic echocardiography carried out on the second day of hospitalization showed diffuse hypokinesis of wall motion. He was diagnosed with catecholamine-refractory hypotension. Despite treatment with glucagon, his blood pressure and heart rate gradually decreased, and he died on the third day of hospitalization. After his death, his serum DPH concentration at the time of arrival was found to be 18.7 μg/mL.

DISCUSSION

DIPHENHYDRAMINE OVERDOSE CAN be fatal.[1] Peak serum levels of DPH are reached approximately 2–3 h after ingestion, and elimination half-life is approximately 4 h. Because DPH is liposoluble and its volume of distribution is large (3–7 L/kg),[2] its elimination by hemodialysis and hemoperfusion is difficult. Although DPH is considered as a relatively safe drug with a large therapeutic range, it causes dose-dependent toxicity. Eckes *et al.*[1] have reported serum DPH concentration of >5 μg/mL as fatal.

Diphenhydramine binds to the H1 histamine receptor and suppresses inflammation and respiratory secretion. It also binds to muscarinic and dopamine receptors. The effects of DPH on delayed rectifier potassium channels of the heart include prolongation of the QT interval and flattening of the T-wave.[3] Moreover, DPH inhibits fast sodium channels of the His–Purkinje system. It delays depolarization, which results in the prolongation of QRS time and bundle branch block.[3]

Eckes *et al.*[1] reported that pulmonary congestion is frequently seen in autopsies of patients with DPH overdose, which is associated with increased vascular permeability.[4]

Table 1. Laboratory analyses at admission of a 45-year-old man with cardiac arrest caused by diphenhydramine overdose

Hematology		Blood sugar	335 mg/dL
White blood cells	11,400/μL	Ethanol	<3.0 mg/dL
Hemoglobin	12.4 g/dL	Troponin I	0.56 ng/mL
Hematocrit	41.6%	Myoglobin	>5000 ng/mL
Platelets	12.5 × 10^4/μL	**Coagulation**	
		PT-INR	1.15
		D-dimer	57.3 μg/mL
Blood chemistry		Fibrinogen	144 mg/dL
Aspartate aminotransferase	336 IU/L	**Arterial blood gas analysis (O_2 10 L/min)**	
Alanine aminotransferase	338 IU/L	pH	6.773
Lactate dehydrogenase	730 IU/L	$PaCO_2$	76.4 mmHg
Creatine kinase	5489 IU/L	PaO_2	407 mmHg
Blood urea nitrogen	16 mg/dL	Bicarbonate	10.5 mmol/L
Creatinine	1.66 mg/dL	Base excess	−26.1 mmol/L
C-reactive protein	0.71 mg/dL	Lactate	156 mg/dL
Sodium	143 mEq/L	**Urine**	
Potassium	5.4 mEq/L	Triage DOA	Negative
Chloride	98 mEq/L		

DOA, Drugs of Abuse; PT-INR, prothrombin time – international normalized ratio; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

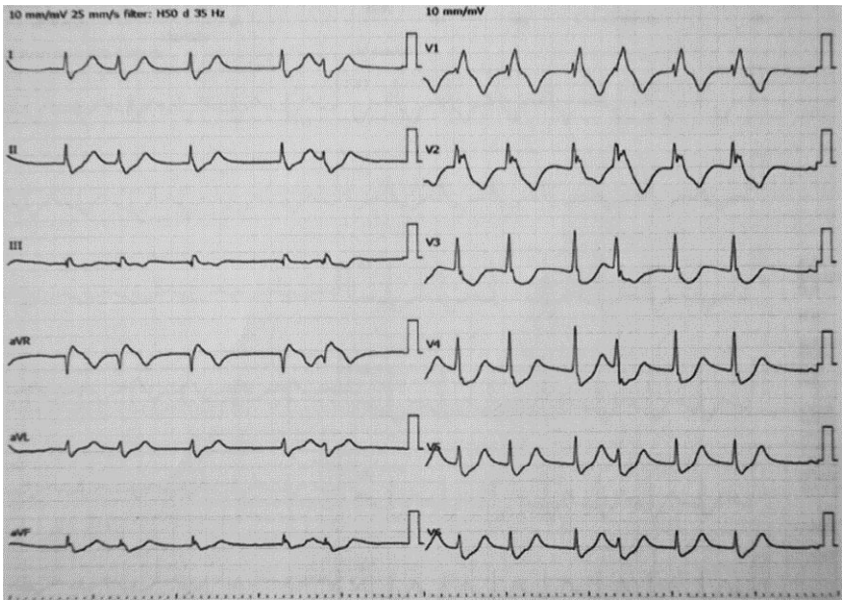

Fig. 1. Electrocardiogram at admission of a 45-year-old man with cardiac arrest caused by diphenhydramine overdose. The trace shows junctional rhythm but QTc was unable to be evaluated because of complete right bundle brunch block.

There is a report of pulmonary edema caused by DPH overdose.[4] In this case, however, CT scan showed no evidence of pulmonary complication. Therefore, the hypoxemia at initial evaluation in the emergency department was considered to be due to the post-cardiac arrest status.

In previous reports, DPH overdose resulted in severe symptoms within several hours.[5,6] Symptoms are dose-dependent. Severe symptoms (delirium/psychosis, seizures, and coma) can occur with ingestion of >1.0 g DPH. The frequency of coma and seizures may increase with ingestion of >1.5 g DPH, and electrocardiographic disturbances may occur with ingestion of >3.0 g DPH.[7] Although the serum DPH concentration was thought to have peaked about 13 h before arriving at the hospital in this case because peak serum DPH concentration is usually reached 2–3 h after ingestion, the patient's serum DPH concentration at the time of arrival was >5 μg/mL, which is considered to be a fatal dose.

Although the patient ingested a fatal dose of DPH, it is estimated that it took approximately 16 h for symptoms to appear. Therefore, caution should be exercised when symptoms occur long after DPH ingestion.

To the best of our knowledge, although immunoassay screening of DPH has been reported,[8] there is no procedure for its rapid measurement, such as application of a kit, in the emergency department. Therefore, screening for DPH overdose and judging the toxic range are difficult. In this case, DPH intoxication could not be diagnosed until the patient died, and DPH was detected in his blood. Clearly, a rapid measurement method is needed for DPH.

Treatments for DPH overdose includes general condition management and symptomatic treatments, such as benzodiazepine (diazepam or midazolam) for convulsions, physostigmine for acetylcholinesterase inhibition, sodium bicarbonate for ventricular arrhythmia, and VA-ECMO for hemodynamic collapse.[4,5,9,10] Although the patient died in this case, it is important to treat unstable hemodynamics with invasive auxiliary circulation such as VA-ECMO.

Intravenous lipid emulsion treatment has been validated for DPH overdose;[6,11] however, its use is controversial.

In this case, rhabdomyolysis was also detected. Rhabdomyolysis due to DPH overdose is usually caused by secondary consequences (e.g., seizure, agitation, and muscle compression due to coma); however, the influence of DPH overdose in inducing direct myotoxicity is unclear.[12] In this case, no hypothermia, hyperthermia, or seizures were observed. Although environmental factors, such as going into the sea in winter, and cardiac arrest and CPR are listed as potential causes of rhabdomyolysis, no such association could be identified.

CONCLUSION

ALTHOUGH DPH IS relatively safe for wide use as an OTC drug, it causes dose-dependent toxicity and may

be fatal if overdosed. As fatalities occur despite intensive care, further studies are required to develop early detection systems such as rapid measurement of DPH and specific treatments for DPH overdose.

DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained from the patient's family for publication of this case report and accompanying images.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None declared.

REFERENCES

1 Eckes L, Tsokos M, Herre S, Gapert R, Hartwig S. Toxicological identification of diphenhydramine (DPH) in suicide. Forensic Sci. Med. Pathol. 2013; 9: 145–53.
2 Paton DM, Webster DR. Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin. Pharmacokinet. 1985; 10: 477–97.
3 Zareba W, Moss AJ, Rosero SZ, Hajj-Ali R, Konecki J, Andrews M. Electrocardiographic findings in patients with diphenhydramine overdose. Am. J. Cardiol. 1997; 80: 1168–73.
4 Kamijo Y, Soma K, Sato C, Kurihara K. Fatal diphenhydramine poisoning with increased vascular permeability including late pulmonary congestion refractory to percutaneous cardiovascular support. Clin. Toxicol. 2008; 46: 864–8.
5 Sharma AN, Hexdall AH, Chang EK *et al.* Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. Am. J. Emerg. Med. 2003; 21: 212–5.
6 Abdi A, Rose E, Levine M. Diphenhydramine overdose with intraventricular conduction delay treated with hypertonic sodium bicarbonate and i.v. lipid emulsion. West. J. Emerg. Med. 2014; 15: 855–8.
7 Radovanovic D, Meier PJ, Guirguis M *et al.* Dose-dependent toxicity of diphenhydramine overdose. Hum. Exp. Toxicol. 2000; 19: 489–95.
8 Rodrigues WC, Castro C, Catbagan P *et al.* Immunoassay screening of diphenhydramine (Benadryl®) in urine and blood using a newly developed assay. J. Anal. Toxicol. 2012; 36: 123–9.
9 Burns MJ, Linden CH, Graudins A *et al.* A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann. Emerg. Med. 2000; 35: 374–81.
10 Scharman EJ, Erdman AR, Wax PM *et al.* Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin. Toxicol. (Phila) 2006; 44: 205–23.
11 Yu JH, Chen DY, Chen HY *et al.* Intravenous lipid-emulsion therapy in a patient with cardiac arrest after overdose of diphenhydramine. J. Formos. Med. Assoc. 2016; 115: 1017–8.
12 Vearrier D, Curtis JA. Case files of the medical toxicology fellowship at Drexel University. Rhabdomyolysis and compartment syndrome following acute diphenhydramine overdose. J. Med. Toxicol. 2011; 7: 213–9.