Key words : drug toxicity, metabolic acidosis, fatal

Severe metabolic acidosis due to intoxication with diphenhydramine

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Abstract

Diphenhydramine is one of the safest drugs among histamine H1-receptor antagonists. An overdose of diphenhydramine induces severe complications. In addition, fatal acute poisoning due to diphenhydramine has occurred. In this report, we discuss a patient with a reduced consciousness level, confusion, and poor orientation and memory. The body temperature was 38.2 degrees C and systolic blood pressure was 176 mmHg. His heart rate was regular at 182 beats per minute, and the respiratory rate was 22 per minute. An electrocardiogram showed sinus tachycardia. Analysis of arterial blood gas demonstrated respiratory compensation of metabolic acidosis. For the initial treatment, we performed the intravenous infusion of lactated Ringer's acetate solution at 15 ml/kg/h, while 1 mEq/kg of sodium bicarbonate was injected over 10 minutes. After 90 minutes of hydration, acidosis was alleviated. On day 3, the serum creatine kinase level was elevated and he was diagnosed with rhabdomyolysis. The serum CK level gradually decreased. In general, ingestions above 1.0 g risk causing severe symptoms, and our case took 1.25 g, leading to a life-threatening situation. Metabolic acidosis is one of the most frequent complications due to diphenhydramine overdose. Increased vascular permeability and vasodilation could be induced by toxicities. From this case report, we suggest the importance of rapid circulation recovery. We should not overlook late complications after recovery from the general condition.

Introduction

Diphenhydramine is one of the safest drugs among histamine H1-receptor antagonists. Diphenhydramine named Drewell@, containing diphenhydramine at 25 mg per tablet in Japan is effective for insomnia[1]. Overdose of diphenhydramine induces generalized convulsions, delirium, and involuntary choreic movements[2]. In addition, fatal acute poisoning due to diphenhydramine has occurred not only in a child[3] but also in a Japanese adult[4]. The peak plasma concentration of diphenhydramine after a single 50-mg oral intake was found to be 0.083 mg/L at 3 hours[5]. A fatal dose in adults was estimated to be 20 to 40 mg/kg[1)~3)], and a plasma concentration above 5 microg/mL[6].

Case report

A 30-year-old man was transferred to the

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emergency department of Matsuyama Red Cross Hospital at 4:55 PM on October 3, 2008. On arrival, the patient showed a reduced consciousness level, confusion, and poor orientation and memory. The fluctuating mental state led to poor communication with the patient. There was no pallor, jaundice, or cyanosis. He showed signs of tachypnea (respiratory rate, 22 breaths/minute). Physical examinations showed that the body temperature was 38.2 degrees C, systolic blood pressure was 176 mmHg, diastolic blood pressure was 87 mmHg, heart rate was regular at 182 beats per minute, respiratory rate was 30 per minute, and SpO2 was 98% in room air. An electrocardiogram showed sinus tachycardia with a QTc interval of 431 ms (**Fig. 1**). Echocardiography showed no abnormality of kinetic wall motion of the left ventricle. Analysis of arterial blood gas demonstrated respiratory compensation of metabolic acidosis (**Table 1**). The serum anion gap was elevated to 41.3 mmol/L. A urine toxicology screen was used to measure phencyclidine, barbiturates, amphetamine, cocaine metabolites, tricyclic antidepressants, opiates, marijuana metabolites, and benzodiazepines, but all were negative (Triage DOA, Biosite Diagnostics, San Diego, CA in USA). The results of the blood chemistry examinations are shown in Table 1. A diagnosis of circulatory collapse and metabolic acidosis was made. For the initial treatment, we performed the intravenous infusion of lactated Ringer's acetate solution at 15 ml/kg/h, while 60 mEq (1 mEq/kg) of sodium bicarbonate was injected over 10 minutes. After 90 minutes of hydration, blood gas analysis revealed pH 7.395, pCO2: 29.2 mmHg, PO2: 104.5 mmHg, BE: −5.8 mmol/L. Diazepam (2 mg) was administered intravenously 2 times for sedation due to irritability, which was ineffective. The patient deteriorated into involuntary choreic movements. At 7:40 PM, he entered the intensive care unit and was endotracheally intubated under sedation. He was kept on hydration with crystalloid at 100 ml/hr. About 12 hours later, we discontinued the sedative drugs. We then confirmed that his consciousness had recovered and his endotracheal tube was

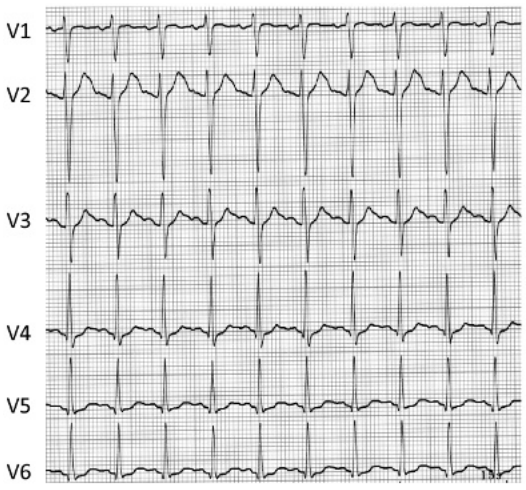

Fig. 1 Electrocardiogram on admission showed sinus tachycardia.

Table 1 Laboratory data on admission

Peripheral blood count			Blood chemistry		
WBC	16250	μl	T-P	9.1	g/dl
RBC	527	x10⁴/μl	T-bil	1	mg/dl
Hb	17.5	g/dl	AST	36	U/l
Ht	51.3	%	ALT	65	U/l
MCV	97.3	fl	LDH	284	U/l
Platelet	33.6	x10⁴/μl	ALP	261	U/l
Coagulation			Amy	68	U/l
PT	13	sec	CPK	219	U/l
PT%	81.9	%	BUN	6.4	mg/dl
aPTT	27.5	sec	Cr	0.87	mg/dl
Arterial blood gas			Na	146	mEq/l
PH	7.039		K	3.9	mEq/l
PaCO2	25.2	mmHg	Cl	102	mEq/l
PaO2	101	mmHg	Glu	111	mg/dl
HCO3	6.6	mEq/l	CRP	0.11	mg/dl
BE	−22.6	mEq/l			
SaO2	95.5	%			

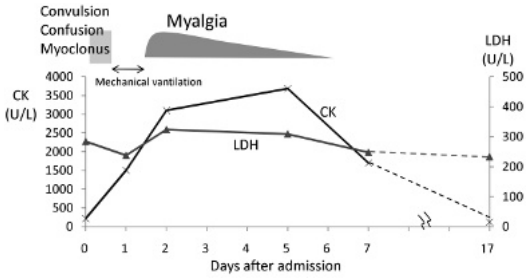

Fig. 2 The clinical course was shown. After recovery from unconsciousness, the serum CK level gradually elevated. He was administered hydration daily and the CK began to fall.

removed. A family member found out a lot of empty medication boxes of Drewell® tablets. He had a history of insomnia during the past week. Although the recommended daily dose of Drewell® for adults is 2 tablets per day, he took 50 tablets on that day at around 3:00 PM. He had no history of abusing other drugs or alcohol. He felt myalgia of the extremities. The serum creatine kinase value was elevated to 1,502 U/L (**Fig. 2**). On day 3 after hospitalization, the serum creatine kinase level was 3,102 U/L, aldolase level was 18.2 U/L, and myoglobin level was 110 ng/mL. He was diagnosed with rhabdomyolysis, and was administered hydration using lactated Ringer's solution (1,000 mL) daily to protect the kidneys. On day 5 after hospitalization, the creatine kinase value peaked at 3,687 U/L, aldolase level to 27.2 U/L, and the myoglobin level was 240 ng/ml. Two days later, creatine kinase began to fall, and all data had normalized two weeks later.

Discussion

This case showed severe symptoms of diphenhydramine overdose. In general, ingestions above 1.0 g risk causing severe symptoms[7], and our case took 1.25 g, leading to a life-threatening situation. Metabolic acidosis is one of the most frequent complications due to diphenhydramine overdose. One reason is that the disturbances of consciousness and generalized convulsions lead to circulation failure as a result of increased lactate production. Increased vascular permeability and vasodilation could be induced by the complete blockade of histamine H1-receptors leading to H2-receptor stimulation due to the massive release of histamine[8]. Dinordiphenhydramine, one of the metabolites of diphenhydramine, is chemically similar to histamine. The metabolites of diphenhydramine could also promote vascular permeability and vasodilation[4]. The abnormal electrocardiogram is caused mainly by the inhibition of fast sodium channels[9]. Over half of the cases of diphenhydramine overdose showed tachycardia[7]. Further, prominent vascular permeability and vasodilation have led to intravascular collapse and circulation failure, which is also the cause of metabolic acidosis. Owing to these mechanisms, our patient developed hyperdynamic heart kinetics to compensate for changes in the circulation. From this case report, we suggest the importance of rapid circulation recovery. Our case underwent the rapid infusion of crystalloid fluids with sodium bicarbonate while monitoring the heart kinetics. In general, crystalloids are preferred for fluid resuscitation in critically-ill patients[10]. There was a diphenhydramine toxic case reported, who was successfully managed with infusion therapy[9]. In addition, one of the complications of an diphenhydramine overdose was revealed to be severe rhabdomyolysis, which could also be lethal[4]. Our case also showed rhabdomyolysis which progressed slowly. Hence, we should not overlook this type of late complication after recovery of the general condition.

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ジフェンヒドラミン大量服薬により重篤な代謝性アシドーシスをきたした一例

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症例は30歳男性，意識障害にて救急外来へ搬送．JCS100，混迷，四肢の不随意運動あり，体温38.2度，血圧176/87 mmHg，心拍数182/min，呼吸数22/minであった．著しい代謝性アシドーシスを呈していた．原因はDiphenhydramineの大量服用と判明した．直ちに細胞外液で輸液を行い循環動態が落ち着いて，なおも意識障害や不穏が続くため，ICUにて鎮静目的に人工呼吸管理を施行した．翌日抜管し，意識状態清明となった．遅れてCPK値の上昇がみられた．Diphenhydramineの大量服用は，本症例でみられるように，意識レベルの異常，循環虚脱による著しい代謝性アシドーシスと過換気，不随意運動，そして横紋筋融解を合併し，しばしば致死的となる．特徴的な症状から中毒の原因を見出しつつ，初期治療として循環虚脱に対処してゆく必要がある．横紋筋融解といった遅発性合併症にも注意が必要である．

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