American Journal of Emergency Medicine 57 (2022) 236.e1–236.e3

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Chlorpheniramine poisoning as a potential cause of rhabdomyolysis

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ARTICLE INFO

Article history:
Received 13 February 2022
Received in revised form 21 March 2022
Accepted 7 April 2022

Keywords:
Chlorpheniramine
Poisoning
Rhabdomyolysis
Case report

ABSTRACT

Chlorpheniramine is an H1 receptor antagonist of the alkylamine class. It is a widely used anti-allergy drug due to its strong antihistamine effect and mild adverse effects. In the case of chlorpheniramine overdose or poisoning, the primary manifestation is central nervous system symptoms. To date, no case of rhabdomyolysis induced by acute poisoning with chlorpheniramine has ever been reported. This study reports a case of acute chlorpheniramine poisoning at an oral dose of 4000 mg, which is the highest reported poisoning dose to date. The diagnosis of rhabdomyolysis (creatine kinase, 195,489 U/L) and acute kidney injury (serum creatinine, 150.1 umol/L) was confirmed based on laboratory results. After haemoperfusion and continuous renal replacement therapy, the patient's renal function fully recovered. This paper aims to analyse the clinical data of this patient and summarize its clinical characteristics. At the same time, the mechanism of chlorpheniramine-induced rhabdomyolysis is also explored in the context of the literature review.

1. Introduction

Rhabdomyolysis syndrome (RM) is a clinical syndrome involving the rapid dissolution of damaged or injured skeletal muscle due to various causes. This leads to the direct release of intracellular muscle components, including creatine kinase (CK) and serum myoglobin (MYO), into the circulation, causing disturbances in the internal environment and even acute renal failure [1]. The classic presentation is myalgia, muscle weakness and dark tea-coloured urine (myoglobinuria) [2]. RM has a variety of pathogenic factors, complex pathological mechanisms and atypical clinical presentation, making it difficult to detect at early stage and highly susceptible to underdiagnosis and misdiagnosis [3].

Chlorpheniramine is one of the most classical H1-antihistamines (AHs) [4] and is commonly used in China for various allergic reactions due to its intense antihistamine action and mild adverse effects. In some Asian countries, chlorpheniramine is also a widely used anticholinergic drug in many non-prescription combined medicines [5]. Meanwhile, chlorpheniramine is a common component of over-the-counter cold and cough medications in some countries [6,7]. These drugs are frequently abused because they are legal, cheap and readily available over the counter. Cases of overdose or poisoning with chlorpheniramine have been reported, with toxicity manifesting itself mainly as central nervous system (CNS) depression followed by euphoria, which can lead to seizures and convulsions [8], and finally produce life-threatening exhaustive CNS depression [9,10].

To date, no cases of chlorpheniramine-induced RM have been reported. This paper reports a case of RM and acute kidney injury (AKI) following acute intoxication with high oral doses of chlorpheniramine. We analysed the clinical data, studied its clinical features, and summarised the successful resuscitation experience. In addition, the mechanism how chlorpheniramine causes RM is discussed in relation to the literature.

2. Case report

A 34-year-old male with no apparent previous medical history self-administered 4000 mg of chlorpheniramine maleate orally during a suicide attempt. There were ten empty bottles of chlorpheniramine maleate (100 tablets per bottle, 4 mg per tablet) at the scene when his family found him and no residual tablets were seen. Within 15 min, the patient developed shortness of breath, palpitations, nausea, and vomited a small amount of the drug after self-induced vomiting. About half an hour later, the patient progressed to delirium and babbling, and was rushed to the Emergency Department of the First Affiliated Hospital of Fujian Medical University (Fujian, China) with “acute drug poisoning (chlorpheniramine)”. His vital signs were as follows:

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https://doi.org/10.1016/j.ajem.2022.04.010

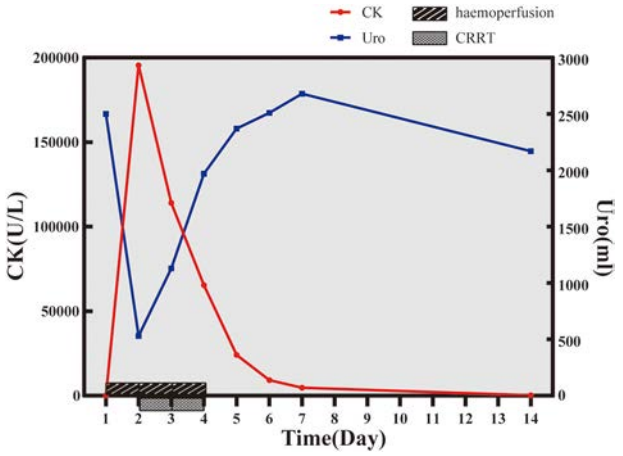

Fig. 1. Changes in urine output (Uro) and creatine kinase (CK) levels during the treatment of rhabdomyolysis-related acute kidney injury in a 34-year-old male who was acutely poisoned after taking high doses of chlorpheniramine orally.

blood pressure, 178/86 mmHg; heart rate, 150 beats/min; respiratory rate, 26 breaths/min; and body temperature, 36.8 °C. He was moody and agitated, but his answers were to the point. The pupils were approximately 3.5 mm bilaterally, and his reflex to light was sensitive. Other systemic investigations, including the neurological system, showed no significant abnormalities. Laboratory findings were normal and did not suggest RM, AKI or other organ function abnormalities. The electrocardiogram indicated sinus tachycardia.

On admission, continuous vital signs monitoring, gastric lavage with water, oxygen inhalation, fluid replacement and diuresis were immediately administered. One hour later, the patient developed a seizure characterized by loss of consciousness, clonic twitching of the extremities, rolling of the eyes and cyanosis of the lips, diazepam 10 mg was immediately administered intravenously. After 2 min, the patient's convulsions stopped, and he was noted to be drowsy. Because of the high dose of drug intoxication (the highest dose reported to have been ingested), the patient was immediately treated with bedside haemoperfusion (Disposable hemoperfusion, Jafro HA330, Jafron Biomedical Co., Ltd). The patient suffered another three further seizures during his hospital stay, each lasting 1 to 2 min, which were terminated by intravenous diazepam or resolved on their own.

About 24 h after admission, the patient began to experience a decrease in urine output (Uro) to about 30 ml/h, with tea-coloured urine, but no significant myalgia or muscle weakness. Laboratory findings confirmed the diagnosis of RM and AKI as follows: creatinine (CREA) 150.1 umol/L, lactate dehydrogenase (LDH) 5962 U/L, creatine kinase (CK) 195,489 U/L, and Creatine kinase isoenzyme (CK-MB) 1176 U/L, alanine aminotransferase (ALT) 126 U/L, aspartate aminotransferase (AST) 623 U/L, potassium ion (K^+) 4.43 mmol/L, serum myoglobin (MYO) >1000μg/L. Due to the patient's critical conditions, he was transferred to the intensive care unit (ICU) for resuscitation and treatment. The patient was treated with continuous renal replacement therapy (CRRT) for two days and intermittent haemoperfusion treatment four times (each lasting 2 h at 12-h intervals), followed by a gradual return to typical mental and vital signs, no recurrence of convulsions, and the Uro recovered to about 100–150 ml/h with clear urine colour. Therefore, the haemoperfusion and CRRT were stopped, and the treatment was continued with fluid replacement, urinary alkalinization and diuresis.

The patient recovered well, his Uro was maintained at 2300-2800 ml/day, and the CK levels decreased on recheck (Fig. 1). He was transferred out of the ICU on the 7th day and was discharged on the 14th day after admission, with complete normalisation of relevant parameters at discharge (Table 1).

The patient received intermittent haemoperfusion treatment four times (lasting 2 h at 12-h intervals) and continuous renal replacement therapy (CRRT) for two days. The Uro recovered to about 100–150 ml/h with clear urine colour and a progressive decrease in CK levels.

3. Discussion

According to previous reports in the relevant literature, most overdoses of chlorpheniramine are 200 mg to 2400 mg [11]. The oral dose, in this case, was 4000 mg, which is the highest reported dose for acute poisoning with chlorpheniramine. Chlorpheniramine poisoning usually begins with symptoms of central depression, followed by symptoms of central excitation, even seizures and convulsions, and finally, a state of CNS depression, which may endanger respiratory and circulatory functions [12]. In this case, the patient took an extreme dose orally and was presented on admission with symptoms of central excitation, such as shortness of breath, rapid heart rate, high blood pressure and recurrent epileptic seizures. Despite aggressive treatment with gastric lavage, haemoperfusion, and volume resuscitation within the first 24 h, the patient developed tea-coloured urine, which, combined with laboratory tests, suggested a significant increase in CK, CK-MB, LDH, AST, ALT and MYO, leading to a clinical diagnosis of RM. At the same time, the patient had a significant increase in CREA level within 24 h (>26.2umol/L) with a decrease in Uro (<0.5 ml/kg·h), which was regarded as AKI associated with RM. No case of RM and AKI induced by acute poisoning with chlorpheniramine has ever been reported.

RM is the immediate release of intracellular components, including MYO, CK, LDH, aldolase and electrolytes, into the bloodstream due to disruption of the integrity of skeletal muscle, leading to a range of clinical manifestations [1]. Rhabdomyolysis is usually caused by direct traumatic injury but can also result from other underlying causes such as drugs, toxins, infections, genetic disorders, exertion or prolonged bed rest [3]. Clinically, RM manifested as myalgia, muscle weakness and myoglobinuria (typical pigmenturia without haematuria) [2]. However, in the early stage of the disease, the characteristic triad of symptoms are observed in less than 10% of the patients, while more than 50% of the patients show only discoloured urine without muscle pain or weakness [3]. As a result, RM is easily missed and misdiagnosed in clinical practice. CK is the most sensitive indicator of myocyte damage. It starts

Table 1
Changes in indicators related to rhabdomyolysis and acute kidney injury during hospitalisation.

Variable/Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14
CREA(umol/L)	77.2	150.1	110.0	109.1	129.0	126.0	132.0	92.0
CK(U/L)	157	195,489	114,061	65,434	24,150	9178	4748	233
CK-MB(U/L)	9	1176	2363	1572	622	135	63	19
LDH(U/L)	226	5962	9031	1885	589	405	288	272
ALT(U/L)	45	200	1033	277	226	239	205	42
AST(U/L)	32	623	1396	605	294	230	124	25
MYO(ug/L)	…	>1000	>1000	>1000	>1000	>1000	595.29	77.28
Urine Output(ml)	2500	530	1130	1970	2370	2510	2680	2170

Note: "… "indicates that the data was not measured. The patient was not considered to have a combination of rhabdomyolysis on admission, and therefore serum myoglobin was not routinely tested.

to rise 12 h after muscle injury, peaks in 1–3 days and starts to fall in 3–5 days [13]. A slow decline is often indicative of progressive muscle damage [13]. When the CK levels exceed five times the upper limit of the normal range and the cause of RM is present, a diagnosis of RM is suggested [14].

Non-traumatic rhabdomyolysis is a rare adverse consequence of drug and toxin overdose or intoxication. No case of chlorpheniramine-induced RM has ever been reported, but some instances of RM induced by AHs, such as doxylamine [15,16] and diphenhydramine [17,18], have been reported. Furthermore, previous cases of acute chlorpheniramine poisoning have been reported in combination with elevated CK levels, suggesting that mild muscle damage may be present but have not yet caused RM. Therefore, chlorpheniramine, one of the most classical H1-AHs, has the potential to induce RM.

The mechanism of AHs induced RM is uncertain. Currently, it is hypothesized that AHs can alter the permeability of the myocyte membrane, causing leakage of intracellular contents and impairment of the Na-K-ATPase pumps and ATP-dependent calcium channels, resulting in intracellular calcium accumulation [19]. These mechanisms lead to excessive myofibril contraction and impairment of energy-dependent processes, ultimately leading to myocyte damage and resulting in RM. [20] On the other hand, seizures induced by chlorpheniramine poisoning may also lead to RM. However, RM due to epilepsy is uncommon, except in persistent epilepsy [21], in which the mechanism is mainly due to muscle damage caused by repeated overstretching of myofibres. Although this patient had recurrent epileptiform seizures, the duration of each attack was short (terminated in 2–3 min). Therefore, it is more likely that RM was caused by the drug itself rather than by a chlorpheniramine-related seizure.

AKI is the most severe complication of RM, with an incidence of 13% to 50% [22]. Early and aggressive fluid resuscitation to restore renal perfusion and increase urinary flow rate is considered the primary intervention for AKI [2], and CRRT may be given if necessary. Delayed diagnosis and treatment may lead to irreversible renal failure. The patient was promptly treated with haemoperfusion to remove the drugs absorbed into the bloodstream and prevent further destruction of myocytes. Meanwhile, the diagnosis and treatment of RM were prompt so that the patient's renal function was eventually fully restored.

4. Conclusion

Our case report aims to suggest the possibility of acute chlorphenamine poisoning inducing RM. This can be missed in the diagnostic process, and physicians should remain vigilant as it may cause serious side effects such as acute renal failure. Because of the potential severity of RM complications and the importance of early diagnosis and treatment to prevent irreversible renal failure, clinicians need to be alert to the possibility of RM when they encounter chlorpheniramine overdose or toxicity.

Credit authorship contribution statement

Qingqing Guo: Writing – original draft, Data curation. **Hao Lin:** Data curation, Writing – original draft. **Jiandong Lin:** Writing – review & editing.

Declaration of Competing Interest

All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part. Additionally, all authors have approved and contributed to the contents of this paper and have agreed to The American Journal of Emergency Medicine submission policies. The named authors have no conflict of interest, financial or otherwise.

Acknowledgement

We thank the patient for kindly providing consent to publish this case. This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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