ABSTRACT

Pheniramine maleate is an easily accessible, over-the-counter antihistaminic, which is frequently involved in overdoses. Pheniramine has antimuscarinic effect causing tachycardia, dilated pupils, urinary retention, and dry flushed skin, and decreased bowel sounds, confusion, mild increase in body temperature, cardiac arrhythmias, and seizures at lethal doses. It has not been implicated as an important cause of rhabdomyolysis and acute kidney injury (AKI). Rhabdomyolysis causing AKI is rarely reported in the literature. This case report emphasizes the occurrence of nontraumatic rhabdomyolysis in pheniramine maleate overdose which required hemodialysis. Since there is a lack of a specific antidote, treatment is mainly symptomatic and supportive. We report a fatal case of a young male with a very high dose of consumption of pheniramine maleate (4.077 g), which was complicated by seizures, respiratory depression, nontraumatic rhabdomyolysis, and AKI. Despite hemodialysis, ventilator support, and other intensive supportive care, patient could not survive and death ensued due to multiorgan dysfunction syndrome.

Key words: Acute kidney injury, convulsions, drug-induced rhabdomyolysis, pheniramine maleate overdose, respiratory depression

INTRODUCTION

Pheniramine maleate is an easily available drug and most commonly used for the treatment of rhinitis and allergic conditions. It is an alkylamine derivative with potent H₁ antagonist less prone than some H₁ antagonists to produce drowsiness and is a more suitable agent for daytime use. Most of the adverse effects are due to its antimuscarinic effect. The clinical features include hallucinations, excitement, athetosis, ataxia, incoordination, and convulsions. Fixed dilated pupils, flushed face, sinus tachycardia, urinary retention, dry mouth, and fever mimics that of atropine poisoning. Terminally, there is deepening coma with cardiorespiratory collapse and death usually within 2–18 h.[1] This case report presents the development of potentially fatal complications including rhabdomyolysis and acute kidney injury (AKI) in pheniramine maleate overdoses.

CASE REPORT

A 25-year-old gentleman brought to the casualty with one episode of generalized tonic-clonic seizures (GTCS) and altered sensorium following consumption of 90 tablets of Avil®50 (pheniramine maleate 45.3 mg/tab), 4 h prior to admission. On examination, patient was in altered sensorium. He was febrile with temperature of 99.6°F, heart rate of 156 bpm, blood pressure (BP) of 110/64 mmHg, respiratory rate of 30 cycles/min and SpO₂ of 50% at room air. Systemic examination revealed tachycardia, tachypnea, rales in bilateral lung fields, tremors, nystagmus, dilated and sluggishly reactive pupil, and excessive sweating. General random blood sugar (GRBS) was 138 mg% and electrocardiogram (ECG) showed sinus tachycardia.
Patient was given stomach wash and was administered 6l/min of oxygen through Hudson’s mask. Despite this, his saturation showed a decreasing trend. In the view of respiratory distress and the falling oxygen saturation, he was intubated and put on synchronous intermittent mandatory ventilation (SIMV). Patient developed two more episodes of GTCS for which intravenous (IV) injection diazepam 10 mg over 5 min was administered and repeated after 10 min. Further as seizures were uncontrolled with diazepam, patient was continuously infused with injection midazolam at a rate of 80 μg/kg/h after a loading dose of 0.2 mg/kg. Since then his seizures were controlled. Laboratory findings on admission were hemoglobin (Hb)-12.5 g%, total count-19,200 cells/mm³, platelets-2.27 lakh/mm³, urea-43.5 mg/dl, creatinine-1.53 mg/dl, electrolytes sodium-146 mEq/l, potassium-3.74 mEq/l, chloride-103 mEq/l, and arterial blood gas (ABG) analysis revealed pH of 7.26, HCO₃⁻ of 18.3 mmol/l, pO₂ of 138 mmHg, and pCO₂ of 31 mmHg. Patient was administered with sodium bicarbonate infusion of 2 mEq/kg IV over 6 h.

Second day patient developed oliguria (360 ml in 24 h) with dark colored urine. Lab investigations revealed Urea-72.6 mg/dl, creatinine-5.4 mg/dl, ABG analysis revealed pH 7.29, HCO₃⁻ 15.9 mmol/l, pO₂ 116 mmHg, pCO₂ 33.1 mmHg, lactate dehydrogenase (LDH)-14,322 U/l, normal urine routine, creatinine phosphokinase (CPK)-254,650 U/l, urine myoglobin-296.75 μg/l, alanine transaminase (ALT)-507 U/l, and aspartate transaminase (AST)-57 U/l. In the view of oliguric renal failure and metabolic acidosis, patient was taken for hemodialysis. Third day he became deeply comatose and developed hypotension with BP of 80/60 mmHg. He was treated with fluid resuscitation. His BP continued to fall further, and hence noradrenaline infusion at a rate of 80 μg/min was started. BP was monitored every 15 min and noradrenaline was then increased every 15 min up to a maximum dose of 12 μg/min. Dopamine infusion was then instituted beginning at a rate of 4 μg/kg/min and titrated for every 15 min up to dosage of 15 μg/kg/min. Laboratory parameters on day 3 were as follows: Urea-124.1 mg%, creatinine-9.84 mg%, sodium-147 mEq/l, potassium-4.62 mEq/l, and chloride-106.3 mmol/l. Patient could not survive despite of various modalities of intensive and aggressive care due to multiorgan dysfunction syndrome.

**DISCUSSION**

Pheniramine maleate is a first generation H₁ antagonist and is the principal antihistamine used in the treatment of allergic conditions. H₁ antagonists inhibit most of the effects of histamine on smooth muscles, especially respiratory smooth muscle constriction. They may produce central nervous system (CNS) depression or stimulation. CNS stimulation; in the form of restlessness, nervousness, and inability to sleep; is occasionally encountered in patients receiving conventional doses. Excitation of CNS commonly results in convulsions, particularly in infants. All the available H₁ receptor antagonists are reversible competitive inhibitors of the interaction of histamine with H₁ receptors. Alkylamine derivatives are among the most potent antihistamines producing more CNS stimulation and less drowsiness. They also have potent competitive inhibition of muscarinic receptors causing anticholinergic side effects. The maximum therapeutic dose of the pheniramine maleate should not exceed 3 mg/kg/day. Our patient had consumed the potentially lethal dose of approximately 4.077 g. Pheniramine is associated with a relatively high incidence of seizures (30%). On chronic usage, it is known to cause autoinduction of hepatic enzymes to develop tolerance to the psychomotor performance and sedative effects.

Rhabdomyolysis is the rapid breakdown of skeletal muscle and leakage of myocyte contents into extracellular compartment due to traumatic or nontraumatic cause. The causes include polymyositis, heat stroke, prolonged convulsions, marathon running, hypokalemia, and viral illness (Epstein–Barr, influenza, and coxsackie viruses). Of late, drugs, including alcohol, have assumed greater importance and in published series have been implicated in up to 81% of cases. Rhabdomyolysis causes myoglobinuria which can lead to AKI, the mechanism of which includes impairment of renal vascular flow due to sympathetic overactivity, activation of the renin–angiotensin system, altered prostaglandin synthesis, high circulating levels of antidiuretic hormone, the deposition of microthrombi, obstruction of tubular lumina by myoglobin casts, direct nephrotoxicity due to ferrihemate (breakdown product of myoglobin at pH < 5.6), and diminished glomerular filtration rate. Among patients with nontraumatic rhabdomyolysis, 33% develop AKI and 15% of them require dialysis. Hampel et al. firstly reported rhabdomyolysis secondary to antihistaminic toxicity leading to renal failure associated with myoglobinuria and CPK value of 30,000 U/l.

Drugs implicated in causing rhabdomyolysis include cimetidine, barbiturates, benzodiazepines, theophylline, and laxatives [Table 1]; among antihistamines, doxylamine and diphenhydramine toxicity have been reported to be associated with rhabdomyolysis. CPK levels ranged from 597 to 78,750 U/l in these cases. Only one case of pheniramine-induced rhabdomyolysis and acute renal failure reported till now.
pheniramine-induced hyperthermia, seizures, and metabolic acidosis.

**CONCLUSION**

Even though many commonly used drugs are implicated in causation of DIR, pheniramine maleate is a very rare drug to cause DIR with only one case having been reported till now. Since it is a very easily accessible, over-the-counter drug which is frequently involved in overdoses, one should be aware of the potential complications including rhabdomyolysis and should anticipate AKI in overdose. This case report emphasizes the occurrence of DIR and AKI as potentially fatal complication. The lack of a specific antidote makes the treatment challenging; and in a very high dose of pheniramine consumption, survival may be unlikely despite early recognition of toxicity.

**REFERENCES**

1. Laurence L, Brunton, John S, Lazo, Keith L, Parker. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 11th ed. San Diego: McGraw-Hill; 2007;24:630-51.
2. Koppel C. Clinical features pathogenesis and management of drug-induced rhabdomyolysis. Med Toxicol Adverse Drug Exp 1989;4:108-26.
3. Curry SC, Chang D, Connor D. Drug- and toxin-induced rhabdomyolysis. Ann Emerg Med 1989;18:1068‑84.
4. Better OS, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med 1990;322:825‑9.
5. Braun SR, Weiss FR, Keller AL, Ciccone JR, Preuss HG. Evaluation of the renal toxicity of heme pigments and their derivatives: A role in genesis of acute tubular necrosis. J Exp Med 1970;131:443‑60.
6. Gabow  PA, Kaehny WD, Kelleher SP . The spectrum of rhabdomyolysis. Med (Baltimore) 1982;61:141‑52.
7. Hampel GA, Horstkotte H, Rumpf  KW. Myoglobinuric renal failure due to drug induced rhabdomyolysis. Hum Toxicol 1983;2:197-203.
8. Frankel D, Dolgin J, Murray BM. Non-traumatic rhabdomyolysis complicating antihistamine overdose. J Toxicol Clin Toxicol 1993;31:493-6.
9. Soto LF, Miller CH, Ognibere AJ. Severe rhabdomyolysis after doxylamine overdose. Postgrad Med 1993;93:227-9, 232.
10. Leybishkis B, Fasseas P, Ryan LF. Doxylamine overdose as a potential cause of rhabdomyolysis. Am J Med Sci 2001;322:48-9.
11. Paul G, Sood P, Paul BS, Puri S. Acute renal failure caused by pheniramine maleate induced rhabdomyolysis: An unusual case. Indian J Crit Care Med 2009;13:221-3.