A Case Of Diphenhydramine With Alcohol Induced Rhabdomyolysis

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Abstract

ABSTRACT

Rhabdomyolysis is muscle necrosis and the release of intracellular muscle components into circulation. Approximately 26,000 cases of rhabdomyolysis are reported annually in the United States. The severity varies greatly from asymptomatic individuals to individuals with life-threatening muscle enzyme elevations along with severe electrolyte abnormalities, acute other organ damage, and compartment syndrome. The mortality rates are as high as 59% in critically ill patients. There are multiple causes of rhabdomyolysis that can be classified as traumatic or non-traumatic. The traumatic cases are usually evident at presentation however, in a non-traumatic setting, the presentation may be misleading. In this specific case report, we discuss a case of rhabdomyolysis with shock liver and acute kidney injury in a 23-year-old male that presented with complaints of back pain and blood in his urine following the recreational use of alcohol and diphenhydramine. Given the frequent use and easy accessibility of both alcohol and diphenhydramine (DPH), it is crucial to be aware of the potential risk of rhabdomyolysis as early recognition and treatment can prevent life-threatening complications.

Keywords
Diphenhydramine, Alcohol, Rhabdomyolysis, toxic, psychosis

Conflict of Interest Statement
The authors declare that they have no conflicts of interest.
Introduction

Rhabdomyolysis is a complex medical condition that involves the release of intracellular muscle components into the circulation as a consequence of muscle injury.\(^1\)\(^2\) Causes of rhabdomyolysis can be classified as traumatic or non-traumatic. The traumatic cases are usually evident at presentation, and non-traumatic etiology presentation may be misleading. The classic presentation includes the triad of skeletal muscle injury, pigmented urine, and renal dysfunction.\(^3\) The use of readily available agents like alcohol and diphenhydramine have been reported in less immediately evident presentations of rhabdomyolysis.\(^4\)\(^5\) We present a case report of a nontraumatic cause of rhabdomyolysis involving the combined use of diphenhydramine (DPH) and alcohol.

Case Presentation

A 23-year-old male with no significant past medical history presented with left-sided back pain and blood in his urine. He was in his usual state of health until about two days earlier when he admitted to excessive alcohol intake and ingesting twenty or more tablets of 25mg of diphenhydramine for recreational use. He reported he had been engaging in strenuous physical activity, which was unusual behavior. He presented with generalized muscle cramps, left sharp non-radiating flank pain starting 2 days prior, and dark color urine. Pain was 10/10, constant, aggravated with movement, but relieved with rest. He reported symptoms associated with nausea, emesis, dark color urine, and acute delirium. He denied the use of other illicit drugs or suicidal or homicidal ideation. On physical exam, his temperature was 37.1°C, blood pressure was 145/88 mmHg, respiratory rate was 18, and his oxygen saturation was 99% on room air. He appeared lethargic but was easily aroused. His pupils were round and reactive to light and anicteric, and he had dry mucosal and a supple neck. His lungs were clear to auscultation. His heart rate was 63 beats per minute with normal S1 and S2 sound and no gallops, rubs, or murmur. The abdomen had normative bowel sound, was soft, non-distended, and had no guarding or organomegaly, but there was tenderness at the suprapubic and costovertebral regions. The genitourinary system showed dark colored urine, and his testes were bilaterally descended and atrophic. His skin was warm, dry, and without a rash. His extremity range of motion was limited due to pain, and there was no ankle pitting edema. He was oriented to person, place, and time, with no motor or sensory deficits. The cranial nerves II-XII were intact. The laboratory findings included a significant serum aminotransferase (AST) of 4066 IU/L (10-40), alanine aminotransferase (ALT) of 685 IU/L (10-49), creatinine of 2.0mg/dL (0.5-1.3), BUN of 27mg/dl (6-18), leukocytosis with 15.9 K/ul (4-11) Hgb of 12.7gm/dl, HCT 41.9%, and elevated LDH with a level of 6150 U/L (84-240). Serum potassium, phosphorus, and calcium were within normal limits. His urinalysis was significant for 3+ moderate blood, but microscopy showed 0-3 RBCs. Given a high degree of suspicion from the urinalysis findings, rhabdomyolysis was suspected, and a creatine kinase (CK) was ordered. This was significantly elevated at 273,740 IU/L (40-308). Serum salicylates, acetaminophen glucose, total bilirubin, alkaline phosphatase, hepatitis panel, and urine drug screen were all normal. Contrast tomography of the abdomen and pelvis was
unremarkable. The findings were consistent with rhabdomyolysis, suspected to be the result of the combined use of alcohol and diphenhydramine; this combined ingestion likely led to a toxic psychosis, causing the patient to engage in excessive physical activity. The patient was admitted to the medical telemetry floor and received aggressive intravenous fluids. His symptoms gradually improved, along with improvement in his renal and liver functions, as shown in the figures below. This correlated with the significant decrease in his CK levels as shown in Figure 1. Before discharge on day 5, the patient was counseled on alcohol cessation in addition to the dangers of combining alcohol with antihistamines.

Figure 1: Creatine Kinase (CK) Progression During Admission

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CREATINE KINASE PROGRESSION

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5
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Figure 2: AST & ALT Progression During Admission

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APARTATE & ALANINE TRANSAMINASE PROGRESSION

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5
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Discussion

Rhabdomyolysis is a striated muscle dissolution or disintegration that can lead to a potentially lethal clinical and biochemical syndrome, with an incidence of approximately 26,000 cases annually in the United States.\textsuperscript{1} Etiology can be either from traumatic or non-traumatic events. Traumatic events such as crush injury are common, while non-traumatic events, including muscle ischemia, hyperthermia, illicit drugs, medications, metabolic derangement, infections, and autoimmune disorders, are uncommon.\textsuperscript{6} It is usually the result of multiple contributing factors that lead to muscle destruction.\textsuperscript{4} In this case, the combination of diphenhydramine combined with alcohol likely triggered the metabolic cascade leading to rhabdomyolysis.

DPH is a first-generation antihistamine that acts as an antagonist at central nervous system histamine receptors, causing drowsiness, cognitive, and psychomotor impairment.\textsuperscript{4} These effects are also modulated by its anti-muscarinic activity, leading to delirium, confusion, and hallucinations. Alcohol acts as a central nervous system depressant, similarly to DPH, and affects cognitive and psychomotor function.\textsuperscript{4} It is postulated that excessive amounts of either substance can lead to prolonged unresponsiveness or comatose states that can indirectly induce muscle injury and uninhibited contraction.\textsuperscript{4,5} The proposed mechanism of injury is that DPH and alcohol alter sarcolemma permeability which leads to leakage of intracellular contents and impairment of NaK-ATPase pumps and ATP-dependent calcium channel, the result of which is excessive myofibril contraction and impairment of energy-dependent process, leading to myocyte injury.\textsuperscript{5} As a result of muscle cell damage, intracellular components are released. Cases
involving direct muscle cell damage by the combinations of DPH and alcohol together as this case presentation are less commonly reported.

The typical presentation of rhabdomyolysis is muscle pain, weakness, and red-to-brown urine.³ The muscle pain is most prominent in the proximal muscle groups.³ Additional symptoms that are commonly seen include nausea, vomiting, fever, and altered mental status, depending on the underlying etiology.⁷ Our patient presented within 48 hours following the ingestion of a high dose DPH and alcohol which led to generalized muscle cramps, worsening left flank pain, dark colored urine, and acute toxic psychosis of excessive physical activity.

An elevation in CK is the most sensitive biomarker for rhabdomyolysis, specifically the CK-MM form found in skeletal muscles.⁶ CK levels begin to rise within 2 to 12 hours, peak between 24 to 72 hours, and levels are usually five times the upper limit of normal at initial presentation.⁸ Non-sensitive markers include lactic dehydrogenase (LDH), aldolase, transaminases, and in severe cases hyperphosphatemia, hyperkalemia, and hypocalcemia.⁶,⁷ There is a disproportional ratio of BUN to Creatinine ratio due to increased formation of creatinine from creatine.⁶ Furthermore, urinalysis finding of dark color is from myoglobin subsequent to muscle injury. Myoglobin is a heme-containing protein that is rapidly excreted in the urine causing the urine to appear dark. This is due to both hemoglobin and myoglobin being indicated as blood on a urine dipstick.⁹ The two can be differentiated with urine microscopy as only a few red blood cells will be seen. The routine testing for myoglobin by urine dipstick evaluation may be negative in up to half of the patients with rhabdomyolysis; myoglobin is rapidly cleared compared to CK which significantly reduces its sensitivity as a marker for the diagnosis of rhabdomyolysis.⁷ In our patient’s case, laboratory findings were significant for elevated CK level of 273,740 IU/L, LDH of 6150 U/L, urinalysis with 3+ moderate blood with microscopy showing 0-3 RBCs, transaminitis (AST) of 4066 IU/L, (ALT) of 685 IU/L, and acute renal injury.

The essential intervention for rhabdomyolysis is vigorous intravenous fluid administration, correcting electrolytes abnormalities, and discontinuing the triggering agent.⁶ The goal of volume repletion is to enhance renal perfusion, remove toxins, and prevent intratubular cast formation from myoglobin. The optimal fluid and rate of repletion is unclear because no studies have directly compared safety and efficacy of the various proposed regimens.¹⁰ It is generally accepted, however, that 1 to 2 L/hour of isotonic saline is the ideal.⁶ All patients should be treated with an isotonic solution until it is clear from sequential laboratory values that the plasma CK level is stable, less than 5000 IU/L, and not increasing.¹⁰ If the level does not decline with appropriate volume expansion, concern for ongoing muscle damage or another differential, e.g., compartment syndrome, should be considered. Additionally, many other agents may play a role in the treatment of rhabdomyolysis.⁶ The administration of bicarbonate aims at urine alkalainization and mannitol enhances renal blood flow and GFR.⁶ However, if fluids, bicarbonate, and mannitol fail to preserve an adequate urine output, loop diuretic or conventional hemodialysis strategies may be beneficial with certain indications.⁶ In our patient's case, initial treatment included a 2 L bolus with
Lactated Ringer’s solution, which was converted to a maintenance fluid rate of 150ml/hr after reaching the desired diuresis rate of 200ml/hr.

**Conclusion**

The prognosis of rhabdomyolysis depends on the extent and severity of muscle injury. Few cases in the literature have reported the effect of the combination of DPH and alcohol as a potential cause of rhabdomyolysis. Although the relationship is not well established, rhabdomyolysis should be considered in the differential diagnosis for a patient presenting with ingestion of DPH and alcohol because of the potential mortality. Early detection and treatment are important for the successful management of rhabdomyolysis to have a favorable prognosis.

**Declaration Of Patient Consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

**Disclaimer**

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