Acta Biomed 2021; Vol. 92, N. Supplement 1: e2021089 DOI: 10.23750/abm.v92iS1.8858 

Case report

# Severe rhabdomyolysis induced by co-administration of cocaine and heroin in a 45 years old man treated with rosuvastatin: a case report

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**Summary.** The term rhabdomyolysis describes a damage involving striated muscle cells or fibers, often complicated by acute kidney injury. This syndrome can have different causes, but it is generally divided into two main categories: traumatic and non-traumatic rhabdomyolysis. Among medical causes, drugs and abuse substances play a pivotal role, being opioids, alcohol, cocaine and other substances of abuse. Among drugs, the case of statins is certainly the best known. Here we describe a paradigmatic case of a man treated with success and good tolerance for years with rosuvastatin, who developed a severe rhabdomyolysis complicated by AKI needing hemodialysis, after the assumption of two substances of abuse (cocaine and heroin). Emergency physicians need to be aware of this syndrome, since it must be clinically suspected in order to ask the Laboratory for appropriate tests. Given that troponins are now widely accepted as the unique biochemical "gold standard" for diagnosing acute coronary syndromes, CK and myoglobin (the "gold standard" tests for diagnosing rhabdomyolysis) have been erased from admission test panels of the vast majority of emergency departments. (www.actabiomedica.it)

**Key words:** rhabdomyolysis, cocaine, heroin, statin, acute kidney injury, creatine kinase

## Introduction

The term rhabdomyolysis describes the rapid breakdown of striated, or skeletal, muscle. As a consequence of the rupture and necrosis of muscle fibers, a release of cell products into the bloodstream and extracellular space takes place. Since skeletal muscles comprises ~40% of the body weight (i.e., several kgs), and the destruction of just 100 g of muscle is capable to induce the clinical syndrome of rhabdomyolysis, it is easy to understand that this "breakpoint" can be reached quite easily (1).

The real incidence of rhabdomyolysis is unknown, mainly due to the fact that many mild (i.e., oligo-symptomatic or asymptomatic) cases probably are unrecognized. Nevertheless, it has been reported that approximately 26.000 cases of rhabdomyolysis are hospitalized every year in the United States (2). Rhabdomyolysis occurs with a wide spectrum of signs and symptoms, ranging from a completely asymptomatic increase of plasma creatine kinase (CK), through massive increases in blood levels of acute kidney injury (AKI) biomarkers, severe alterations of electrolyte balance and, in the most severe cases, disseminated intravascular coagulation (DIC). There is evidence that the percentage of patients developing AKI secondary to rhabdomyolysis varies from 13% to over 50%, mainly depending on the clinical and organizational setting where it is diagnosed (3).

This syndrome can have different causes, but it is generally divided into two main categories: traumatic and non-traumatic rhabdomyolysis (4). In trauma pa-

tients, it is important to distinguish among the terms rhabdomyolysis, crush injury, compartment syndrome and crush syndrome (3, 5-7). Rhabdomyolysis describes a damage involving striated muscle cells or fibers; crush injury describes all those injuries that occur as a consequence of crushing of bodily parts (usually a limb). Compartment syndrome describes the complications arising due to increased pressure inside one or more muscular compartments (where rhabdomyolysis may, or may not, have occurred) that can cause failure of regional circulation and onset of ischemic injury to nerves and muscles. Crush syndrome describes the complex pathophysiological consequences that may arise due to massive rhabdomyolysis involving kidneys and the coagulation system.

Direct muscle injury remains the most common cause of severe rhabdomyolysis, although this syndrome includes a kaleidoscope of etiological categories, that are frequently overlapped: i) hypoxic, ii) physical, iii) chemical, mainly represented by drugs or substances of abuse, iv) biological (8).

Among medical causes, drugs and abuse substances play a pivotal role, being opioids, alcohol, cocaine and other substances of abuse (9) the most frequently involved. Several cases of cocaine-induced rhabdomyolysis have been described in the past decades, and severity of muscle injury seemingly parallel the severity of cocaine intoxication. Studies of cocaine-intoxicated patients observed in the ED revealed a 5-24% incidence of increased CK activity. These patients may develop rhabdomyolysis in association with other causes, such as seizures, excessive muscle activity, hyperthermia, tissue hypoxia from limb compression following loss of consciousness, and hypovolemia (10, 11). Summarizing, these compounds directly trigger rhabdomyolysis, i.e., through toxic effect on muscle fibers, or indirectly, i.e., through immobilization-compression or muscular hyperactivity (12).

An increasing number of drugs is currently recognized as a possible, or even well established, cause of rhabdomyolysis, both as single therapy or in various associations. Among these, the case of statins is certainly the best known. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins) decrease cholesterol serum levels by inhibiting the enzyme that catalyzes the rate limiting step in cholesterol synthesis. Mechanisms of statin-induced muscle injury are not fully established and are probably multifactorial. Some studies described an association between some genetic polymorphisms and the risk of developing statin-induced rhabdomyolysis (13-16). The clinical spectrum of statin-induced myopathy ranges from asymptomatic elevations of serum CK levels to muscle pain or weakness, up to rhabdomyolysis with muscle symptoms, elevated serum levels of CK and renal damage.

Statin-associated rhabdomyolysis may be enhanced by use of fibrates (15, 17) and may also be modulated by physical exercise (18). Notably, cerivastatin was withdrawn from the market in 2001, when its use was strongly associated with rhabdomyolysis, leading to 31 deaths, 12 of which involved the concomitant use of gemfibrozil.

The laboratory diagnosis of rhabdomyolysis is still essentially based on the measurement of serum or plasma CK, which is considered the most sensitive test despite being a "surrogate" marker. Although there is no established cut-off threshold, a concentration five to ten times the upper reference limit (URL), i.e., ~1000 U/L, is commonly used (1). CK levels increase in the first 12 h, peak on the second or third day and return to baseline 3-5 days later. CK values are generally considered to predict the likelihood of developing AKI, with a concentration >5000 U/L thought to be closely associated with development of kidney damage. Recent evidence has emerged that peak values of myoglobin in serum or plasma could be better predictors of AKI than CK values (19, 20). Importantly, the traditional dipstick methods do not differentiate between hemoglobin, myoglobin or red blood cells. Hematuria is frequently detected in patients with rhabdomyolysis and it could be responsible of false positive results and leading to inappropriate therapeutic management. It may hence be concluded that CK should still be considered the biochemical "gold standard" for diagnosing rhabdomyolysis, whereas myoglobin should be considered the prognostical "gold standard", mainly in patients with non-traumatic rhabdomyolysis.

Here we describe a paradigmatic case of a man treated with success and good tolerance for years with rosuvastatin, who developed a severe rhabdomyolysis complicated by AKI after the assumption of two substances of abuse (cocaine and heroin).

## Case report

A 45 years old man presented to our Emergency Department (ED) complaining for diffuse severe myalgia and weakness. Physical examination showed mental confusion, agitation alternated with drowsiness, oligoanuria, diffuse muscle tenderness, hypotension (90/50 mmHg) and signs of dehydration. No other significant findings on physical examination.

No relevant ECG abnormality were recorded.

The blood tests' results (table 1) were as follows: pH 7.20; $pCO_2$ 25 mmHg; $HCO_3$ 14 mEq/L; creatinine 10.75 mg/dL; potassium 5.6 mEq/L; alanine aminotransferase 1956 U/L; creatine kinase 551820 U/L. There was no significant increase in troponin level.

He admitted to have abused in cocaine and heroin the day before ED admission. He also reported to be on rosuvastatin 10 mg daily since 3 years before due to familial hypercholesterolemia. No other significant features were found in his past medical history.

Renal ultrasound showed a renal cortex thickness slightly reduced.

Muscle pain was managed with morphine infusion (0.1 mg/kg/hour).

We performed a vigorous intravenous fluid replacement by Ringer lactate (500 mL/h) and 5% glucose solution (500 mL/h) alternately, and electrolyte support with calcium gluconate. Furthermore, 8.4% sodium bicarbonate (100 mL, twice) was administered. Due to severe renal failure, the patient was referred to the nephrologist, who decided to perform hemodialysis.

The patient remained oliguric after first hemodialysis treatment, but parameters and clinical conditions improved, despite persistence of severe myalgia (table 1). Serum CK markedly decreased, but remained significantly high.

Ten days later, the patient was still under hemodialysis with renal function and urine output slowly improving (table 1).

## Discussion and Conclusions

The mainstream treatment of rhabdomyolysis stands on a promptly initiated fluid infusion, aimed to maintain a urinary output of 200-300 mL/h. In order to avoid volume overload, it is highly recommended to alternate 500mL of sterile saline solution with 500 mL of 5% glucose solution, adding 50mmol of sodium bicarbonate for each subsequent 2-3 L of solution (usually 200-300 mmol on the first day) and maintaining the urine pH above 6.5 and plasma pH below 7.50 (3). The speed of infusion should be ~500 mL/h, while hemodynamic parameters and urine output should be closely monitored. The role of osmotic agents (e.g., mannitol) or loop diuretics (e.g., furosemide) was never proven to be useful and should hence be discouraged (3). It should also be considered that sodium bicarbonate, targeting urine alkalinization around a pH of 6.5, prevent myoglobin precipitation into the renal tubuli but may also help managing one of the most frequent complications: hyperkalemia eventually associated with metabolic acidosis (3, 21). Forced hydration should be continued until disappearance of myoglobinuria, which typically occurs in the third day. Hyperkalemia must be managed using the usual techniques, considering that treatment with glucose and insulin may be ineffective in this setting due to inability of damaged muscle tissues to catch potassium

**Table 1.** Clinical and laboratory features in rhabdomyolysis patient at baseline and after ED fluid infusion

| Variable | Baseline | After 1st Hemodialysis | 10th day |
|---|---|---|---|
| Urine output (ml) | 0 | 50 | 750 |
| Blood Pressure (mm/Hg) | 90/50 | 120/80 | 110/70 |
| Creatine Kinase (U/L) | 551.820 | 56.130 | 4820 |
| ALT (U/L) | 1956 | 1313 | 745 |
| K (mEq/L) | 5.6 | 5.2 | 4.8 |
| Myoglobin (ng/mL) | 14.193 | 3.856 | 562 |

from the extracellular space, enhancing the importance of sodium bicarbonate infusion. It is often necessary to treat severe hyperkalemia with hemodialysis.

This case is paradigmatic, displaying all the typical clinical features of non-traumatic rhabdomyolysis, thus demonstrating that even when a statin is well tolerated for years, an occasional interaction with other substances can trigger a dramatic cascade of events leading to severe rhabdomyolysis and AKI. Emergency physicians thus need to be aware of this syndrome, since it must be clinically suspected in order to ask the Laboratory for appropriate tests. Given that troponins are now widely accepted as the unique biochemical "gold standard" for diagnosing acute coronary syndromes, CK and myoglobin have been erased from admission test panels of the vast majority of EDs. Troponin concentrations, on the contrary, can be increased in case of severe rhabdomyolysis, possibly reflecting associated myocardial damage (22), particularly when the syndrome is associated with cocaine abuse, due to the well-known detrimental cardiac effects of the substance (23).

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 16 September 2019
Accepted: 19 September 2019
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