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Acute hepatitis secondary to abuse of cocaine, associated with severe rhabdomyolysis

Hepatite aguda secundária ao abuso de cocaína, associada a severa rabdomiólise

José Hícaro Hellano Gonçalves Lima Paiva[1], Vitória Nunes Medeiros[2], Ivelise Regina Canito Brasil[3]

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ABSTRACT: Cocaine is a drug with a noticeable ability to adversely affect almost every organ in the body, and can cause a multitude of secondary multisystem abnormalities. In the present study, we report three cases of acute liver failure complicated by rhabdomyolysis and acute kidney injury following cocaine and alcohol use. Disease onset, clinical manifestations, laboratory data, diagnosis, and treatment of each patient were recorded. The presence of multifactorial causes for the occurrence of liver failure and rhabdomyolysis was noted in the three reported cases. Laboratory tests revealed that serum trasaminases and creatine phosphokinase (CPK) levels increased, and symptoms of acute renal failure were present, which provided an accurate diagnosis of acute liver failure complicated by severe rhabdomyolysis and acute kidney injury requiring dyalisis. Rhabdomyolysis is a condition of hypermyoglobinuria, being one of the main factors that promote deterioration of renal function. Early phase therapy involved support for fluid resuscitation associated with dialysis therapy with strict control of renal function. All three patients developed multiple organ involvement, but only one died due to the severity of the condition. Considering the three cases presented, we conclude that liver failure, complicated by rhabdomyolysis, secondary to cocaine and alcohol use, may have a poor clinical prognosis, depending on several factors. Physicians should be aware of the potential effects caused by cocaine to manage the multiple complications associated with cocaine abuse.

Keywords: Cocaine; Acute kidney injury; Rhabdomyolysis; Liver failure, acute.

RESUMO: A cocaína é uma droga com notória capacidade de afetar adversamente quase todos os órgãos do corpo e pode causar uma infinidade de anormalidades multisistêmicas secundárias. No presente estudo, relatamos três casos de insuficiência hepática aguda complicada por rabdomiólise e lesão renal aguda após consumo de cocaína e álcool. O início da doença, as manifestações clínicas, os dados laboratoriais, o diagnóstico e a terapêutica de cada paciente foram registrados. Nota-se a presença de causas multifatoriais para a ocorrência de insuficiência hepática e rabdomiólise nos três casos relatados. Os testes laboratoriais revelaram que a concentração sérica de transaminases, bem como os de creatinafosfoquinase (CPK) aumentaram e que os sintomas de insuficiência renal aguda estavam presentes, o que forneceu um diagnóstico exato de insuficiência hepática aguda complicada por grave rabdomiólise e lesão renal aguda dialítica. Rabdomiólise é uma condição de hipermioglobinúria, sendo uma dos principais fatores que fomentam uma piora da função renal. A terapia da fase inicial envolveu suporte a ressuscitação volêmica associada a terapia dialítica com rigoroso controle da função renal. Os três pacientes desenvolveram comprometimento de múltiplos órgãos, mas apenas um foi a óbito devido a gravidade do quadro. Considerando os três casos apresentados, concluímos que a Insuficiência Hepática, complicada por rabdomiólise, secundária ao uso de cocaína e álcool pode ter mau prognóstico clínico, a depender de vários fatores. E os médicos devem estar cientes dos potenciais efeitos causados pela cocaína, a fim de gerir as múltiplas complicações associadas ao abuso destas substâncias.

Descritores: Cocaína; Lesão real aguda; Rabdomiólise; Falência hepática aguda.

1. Faculty of Medicine of Ceará State University (UECE), Fortaleza, Ceará, Brazil. ORCID: https://orcid.org/0000-0002-6232-003X. E-mail: hellanohicaro@gmail.com.
2. Faculty of Medicine of Ceará State University (UECE), Fortaleza, Ceará, Brazil. ORCID: https://orcid.org/0000-0003-1621-2385. E-mail: vitoria21nunes@gmail.com.
3. Transplant Service of Hospital Geral de Fortaleza (HGF), Fortaleza, Ceará, Brazil. ORCID: https://orcid.org/0000-0002-4886-7442. E-mail: ivelise.canito@uece.br.

Correspondence: José Hícaro Hellano Gonçalves Lima Paiva. Rua Pão de Açúcar – Nº 114 - Centro – Reriutaba. Email: hellanohicaro@gmail.com.

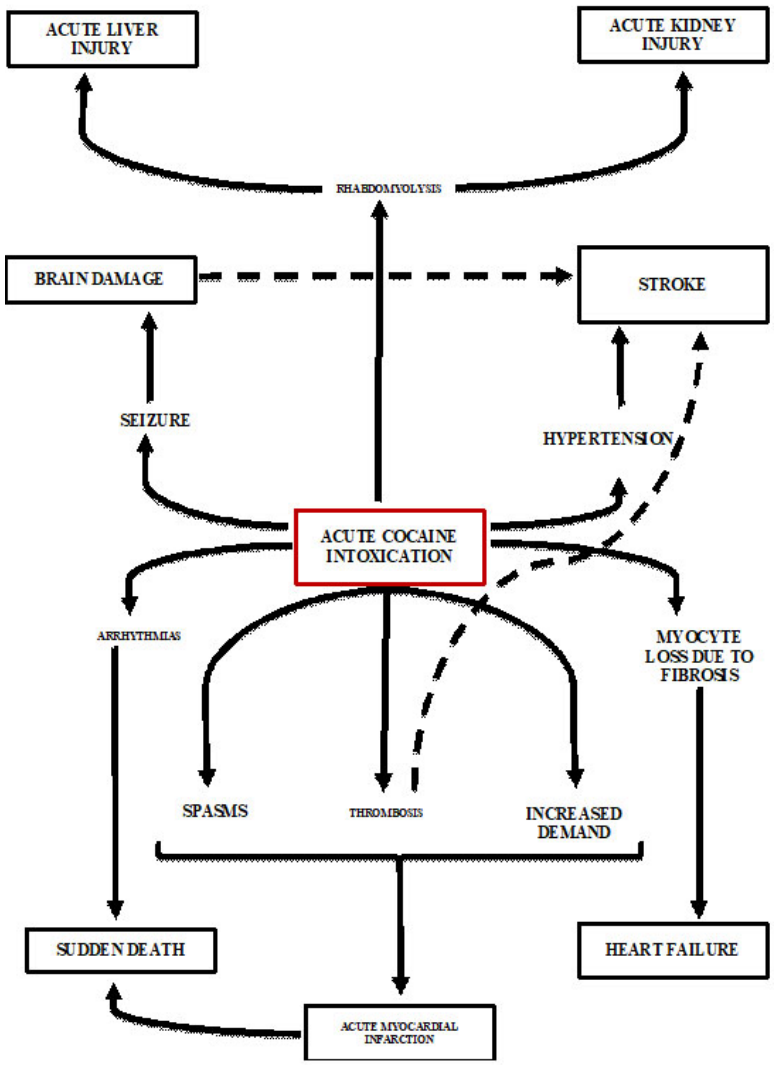
INTRODUCTION

Cocaine intoxication and abuse are a global problem associated with several complications, resulting in high morbidity and mortality among users[1]. Despite the drop in the number of cocaine users between 2007 and 2014, the prevalence of users is significant, with around 18.3 million users worldwide. In this context, the global prevalence of diseases attributable to the use of alcohol and illicit drugs is estimated at around 5.4%[2].

In Brazil, cocaine use is a prevalent condition, and Brazil is one of the main countries responsible for illegal cocaine trade. The use of the substance is more common in the age group of 18 - 24 years[2]. There is a significant increase in cocaine use, despite a reduction in consumption in the United States and relative stability in Europe. The increasing commercialization of cocaine in areas of socioeconomic fragility and with little access to a rehabilitation system is one of the justifications for this increase[3].

The clinical syndrome of patients admitted to emergency departments for cocaine intoxication is characterized by sympathomimetic manifestations (tachycardia, hypertension, agitation, tachypnea, and diaphoresis) and/or systemic manifestations[1].

Acute neurological changes can manifest with fluctuations in the level of consciousness, mania, psychosis, generalized seizures, and strokes. Cardiovascular manifestations can range from acute chest pain, which is the most frequent complaint, to acute aortic dissection[4] and supraventricular or ventricular arrhythmias[1] (Figure 1).



Source: Prepared by the authors.

Figure 1. Complications associated with cocaine use and possible mechanisms

Such conditions allow us to infer about the potential for morbidity and mortality associated with cocaine abuse. Although the effects of cocaine on the aforementioned systems are well documented, little is known about the effects and management of patients with renal and hepatic involvement[5].

Hepatotoxicity is a complication that can occur after using a copious amount of cocaine. Acute liver failure is defined by changes in coagulation parameters and mental status (encephalopathy) in patients without pre-existing cirrhosis and who have the disease for less than 26 weeks[6,7].

The pathogenesis of severe acute hepatitis secondary to cocaine intoxication is still uncertain. However, it is believed that cocaine metabolism results in the accumulation of free radicals in the hepatic system, causing oxidative stress of hepatocytes. In addition, there are other conditions that can act in synergism with cocaine abuse to cause liver damage, such as alcohol abuse, rhabdomyolysis, and the use of other hepatotoxic substances[8,9].

Another important clinical manifestation is rhabdomyolysis, which can have severe and sometimes fatal clinical progression. There are multiple causes associated with rhabdomyolysis, such as trauma, hyperthermia, infections, convulsive disorders, and exogenous intoxications[10]. The clinical presentation of rhabdomyolysis is variable, ranging from asymptomatic to severe cases, and can result in shock, compartment syndrome, acute kidney injury, hydroelectrolytic imbalance, and acid-base disorders[11].

The laboratory diagnosis of rhabdomyolysis is based on the measurement of serum creatine phosphokinase (CPK), which may be normal in the early stages of the clinical picture. However, changes in renal and liver function can be present since the onset of symptoms[12].

OBJECTIVES

The aim of this study was to describe three cases of cocaine-induced severe acute hepatitis complicated by rhabdomyolysis and acute kidney injury in young adult patients.

METHODS

Physical medical records were analyzed for data collection at Hospital Geral de Fortaleza - Fortaleza, Brazil. Patient anonymity was assured.

CASE REPORTS

Case 1

The patient was a 32-year-old man, cocaine and alcohol user since the age of 17, with regular use four times a week. The patient sought medical assistance after using copious amounts of cocaine, i.e., 3.5 grams. On admission, he reported severe myalgia, recent onset mental confusion, and urinary disorders, with darkened urine and decreased diuresis.

On admission, the patient was jaundiced, agitated, disoriented, and with a Glasgow coma scale of 11. Blood pressure was 106x40 mmHg, pulse 56 beats per minute, respiratory rate 18 breaths per minute, oxygen saturation in room air 97%, and temperature 36.3°C. Physical examination revealed diffuse abdominal pain; other systems showed no changes.

Initial laboratory tests revealed an increase in the values of liver enzymes, markers of kidney damage, leukocytes, CPK, and C-reactive protein (CRP). Other laboratory parameters assessed were within the normal range (Table 1).

Intensive care, vigorous intravenous hydration, and monitoring of diuresis were started. However, the patient evolved with worsening azotemia and anuria, and hemodialysis was indicated.

In view of the clinical picture, acute liver failure secondary to cocaine use was the diagnostic hypothesis, according to The American Association for the Study of Liver Diseases criteria. The patient also had acute oliguric renal failure, according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, secondary to severe rhabdomyolysis.

During hospitalization, the patient persisted with temporospatial disorientation, evolving with active bleeding into the eye and from the central venous catheter insertion site. He also had feverish peaks with temperatures of 38°C and leukocytosis with a predominance of polymorphonuclear cells, and the hypothesis of bacterial infection was suggested. Antibiotic therapy with metronidazole and ciprofloxacin was initiated due to clinical suspicion of cholangitis.

Despite intensive care, the patient progressed with hypoglycemia refractory to pharmacological measures, persistent elevation of liver enzymes and bilirubin, thrombocytopenia, and severe anemia. Transfusion of four red blood cell concentrates was necessary, with subsequent improvement of hematological parameters.

On the fifth day of hospitalization, the patient's laboratory parameters worsened and compartment syndrome was suspected. Ultrasound evaluation of the left upper limb was performed and revealed the presence of two hematomas. In view of this, transfusion of a red blood cell was performed, and antibiotic therapy was escalated to meropenem and vancomycin. Antifungal therapy with anidulafungin was started.

Serologies for viral hepatitis and lepstospirosis, factor V Leiden, urine culture, and blood culture were negative. Computed tomography of the skull, chest, and abdomen did not show any significant changes.

In the days following admission, the patient showed

a progressive improvement in clinical and laboratory parameters. As for the need for liver transplantation, an expectant approach was chosen, since King's College criteria were not met. After 29 days of hospitalization, the patient was discharged to continue with outpatient follow-up.

Table 1. Laboratory tests on admission and during hospitalization

	Patient 1				Patient 2			Patient 3				Ref.
Parameters	*1st DOH*	*2nd DOH*	*5th DOH*	*10th DOH*	*1st DOH*	*2nd DOH*	*3rd DOH*	*1st DOH*	*2nd DOH*	*5th DOH*	*10th DOH*	
Potassium (mmol/L)	3.4	2.8	5	3.8	4.3	**	4.9	3.7	5.7	5.3	4.6	3.5-5.3
Sodium (mmol/L)	141	133	132	131	138	137	135	137	140	138	136	135–148
TB (mmol/L)	2.4	3.7	12.08	17.47	**	3.7	4.7	5.72	11.37	15.66	11.06	
DB (mmol/L)	0.7	1.5	7.24	12.2	**	3.2	3.6	3.53	5.05	6.75	8.61	< 1
Urea (mg/dL)	58	82	62	324	81	100	64	147	134	111	175	13–43
Creatinine (mg/dL)	2.9	5.3	5.2	6.7	5.3	6.9	5.5	4.57	7.4	6	7.7	0.6-1.1
AST (U/L)	171	1576	2163	370	**	3105	6179	6720	10020	3205	135	< 32
ALT (U/L)	46	467	3307	411	**	2354	5120	3740	7226	4152	254	< 31
PT (s)	1.47	3.5	1.95	1.22	6	1.82	3	3.53	4.47	1.67	1.04	10–14
aPTT (s)	**	**	1.4	1.46	0.5	**	3.95	1.93	1.77	1.3	1.24	22–28
Lipase (U/L)	113.9	59.6	**	**	**	**	**	**	1495	192	65	13–60
Amylase (U/L)	115	246	**	**	**	**	**	**	616	118	58	< 84
LDH (U/L)	821	3827	**	**	**	**	**	**	**	3784	1989	230–460
CPK (U/L)	3860.6	1230	24388	9194	184328	86865	**	502000	263995	59190	14562	< 170
Hemoglobin (g/dL)	14.4	14.2	5.5	8.4	13.8	11.6	10.9	14.7	12.2	11.6	10.4	11.3-15.2
Leukocytes (/ mm³)	25410	24490	11100	17400	25190	15730	22780	21800	23900	14000	13300	3600–10000
Platelets (/ mm³)	196000	230000	47000	147000	310000	207000	306000	184000	123000	57000	398000	150-450 (10^3)

Caption: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: lactate dehydrogenase; CPK: Creatine phosphokinase; PT: prothrombin time; aPTT: Activated partial thromboplastin time; Ref: Reference; DOH: Day of hospitalization. ** Not assessed
Source: Prepared by the authors

Case 2

The patient was a 33-year-old man, chronic cocaine user, with dyslipidemia. He was admitted to the Intensive Care Unit after cocaine abuse and multiple trauma after a fall from standing height secondary to a psychotic break.

On admission, the patient presented with a decreased level of consciousness and a Glasgow coma scale of 8. Blood pressure was 82x41 mmHg, temperature 36.2°C, pulse 116 beats per minute, and respiratory rate 35 breaths per minute. Physical examination revealed abdominal distension and severe abdominal pain. There were no changes in the other organs and systems.

Initial laboratory tests showed an increase in liver enzymes, markers of kidney damage, and CPK. Other parameters assessed were within the normal range. Admission arterial blood gas analysis showed the presence of compensated metabolic acidosis (Table 1).

In view of the clinical picture, acute liver failure secondary to cocaine use was the diagnostic hypothesis, according to The American Association for the Study of Liver Diseases criteria. The patient also had acute oliguric

renal failure, according to KDIGO criteria, secondary to severe rhabdomyolysis.

Orotracheal intubation was performed, as the patient persisted with hemodynamic instability and with decreased level of consciousness. The patient was started on vasoactive drugs and, for neuroprotection, on sodium bicarbonate. However, clinical and laboratory parameters continued to worsen, despite the interventions. Dialysis therapy was indicated due to anuria and worsening markers of kidney damage.

In the following days, the patient developed refractory hypoglycemia (capillary blood glucose of 48 mg/dL) and worsening laboratory parameters. The liver transplant team evaluated the patient, but after three days of hospitalization, the patient died due to the severity of the clinical condition.

Case 3

The patient was a 38-year-old man, previously hypertensive, alcoholic, smoker (20 packs/year), cocaine and crack user for 20 years. He was admitted to the Intensive Care Unit two days after suffering multiple trauma due to physical aggression and evolving clinically with decreased diuresis and diffuse myalgia. After the episode of aggression, the patient lost consciousness and aspirated mud.

Before the traumatic event, he had used crack and alcohol. He also reported making sporadic use of anti-inflammatory drugs due to constant headaches. About two weeks before admission, he developed the flu and self-medicated with ibuprofen and paracetamol.

On admission, he was jaundiced, with signs of encephalopathy and temporospatial disorientation and a Glasgow coma scale of 10. Blood pressure was 102x57 mmHg, pulse 56 beats per minute, and respiratory rate 20 breaths per minute. There were no changes in the other organs and systems.

Initial laboratory tests revealed an increase in liver function and liver damage enzymes, markers of kidney damage, and CPK (Table 1). Other parameters assessed were within the normal range. Initial arterial blood gas analysis showed the presence of metabolic acidosis Serologies for viral hepatitis and lepstospirosis and blood cultures were negative.

In view of the clinical picture, acute liver failure secondary to cocaine use was the diagnostic hypothesis, according to The American Association for the Study of Liver Diseases criteria. The patient also had acute oliguric renal failure, according to KDIGO criteria, secondary to severe rhabdomyolysis.

Vigorous intravenous hydration and strict control of renal function were started, and dialysis therapy was indicated due to anuria and azotemia. In the following days, the patient evolved with significant pressure peaks, and antihypertensive therapy was optimized. Abdominal ultrasound and renal artery Doppler ultrasound were requested to investigate secondary hypertension, and showed no changes.

The patient was evaluated by the transplant team regarding the need for liver transplantation. However, the patient did not meet King's College criteria.

During hospitalization, he developed abstinence syndrome and lorazepam was started to control symptoms. In the course of hospitalization, the patient's clinical and laboratory parameters improved. After 35 days of hospitalization, the patient was discharged to continue with outpatient follow-up.

DISCUSSION

From the mid-twentieth century on, cocaine became popular, with a significant increase in the use of the drug worldwide. Excessive use of cocaine can affect multiple systems and cause neurological, cardiac, hepatic, renal, and psychiatric changes[13,14].

In the reported cases, clinical and laboratory abnormalities at the time of admission reflected a serious condition, since they were associated with evidence of multiple organ dysfunction. Table 2 describes the clinical features and progress of patients during hospital stay.

Liver damage caused by cocaine has a broad clinical spectrum, ranging from minimal transaminase changes in chronic users to severe acute hepatitis associated with rhabdomyolysis. Concomitant alcohol consumption acts in synergism with cocaine abuse to worsen hepatotoxicity[15].

Cocaine is one of the most illicit drugs co-occurring with alcohol abuse. Cocaine and alcohol combination potentiates cocaethylene formation, enhancing the cardiotoxic and neurotoxic effects of cocaine or alcohol alone[16]. A cross-sectional study with adolescents showed an association of crack-cocaine abuse with alcohol in 43.2% of the crack users[17]. The profile of the patients described in the present study is in line with data described in the literature, since the use of multiple drugs was observed in all three cases.

The diagnosis of severe acute hepatitis was established based on the clinical picture of patients at the time of admission, with less than 24 weeks of evolution, correlated to laboratory tests, in which changes in coagulation parameters and substantial elevation of transaminases, lactate dehydrogenase, and bilirubin were observed.

Liver damage in these patients can be attributed to multiple factors. The three patients were young adults in their thirties and chronic cocaine and alcohol users. This fact can increase acute liver damage. In one of the patients, the indiscriminate use of anti-inflammatory drugs may have contributed to the worsening of the clinical picture.

Table 2. Clinical features and progress during hospitalization

Clinical Features	**Patient 1**	**Patient 2**	**Patient 3**
Length of stay	29	3	35
Gender	M	M	M
Age	32	33	38
Concomitant use of alcohol	Yes	Yes	Yes
Habitual use of cocaine	Yes	Yes	Yes
Complications during hospitalization			
Psychomotor agitation	Yes	Yes	Yes
Acute Renal Failure	Yes	Yes	Yes
Hepatic Encephalopathy	Yes	Yes	Yes
Jaundice	Yes	Yes	Yes
Hypotension	No	Yes	No
Need for vasoactive drugs/OTI*	No	Yes	No
Death	No	Yes	No
Bleeding	Yes	No	No
Acute Pancreatitis	No	No	Yes
Serologies/Cultures			
Hepatitis A	NR	**	NR
Hepatitis B	NR	**	NR
Hepatitis C	NR	**	NR
Blood culture	NR	**	NR
Urine culture	NR	**	NR

Caption: *OTI: Orotracheal Intubation: *NR: Non-reactive
Source: prepared by the authors

Despite the epidemiological context in which the patients are, there is no evidence to explain liver damage as secondary to acute hepatitis and leptospirosis, since these serologies were negative in two patients. In one case, there was no time for serological evaluation, as the patient died three days after admission.

In a study, high levels of aspartate aminotransferase (AST) were associated with the occurrence of acute renal failure and death during hospitalization. There was also a trend toward complications associated with the disease in these patients[13]. Similar results can be observed in this study, since in the three cases described, the values of AST and ALT were increased by more than 20-fold the upper limit of normal, and one of the patients died. These findings may suggest that knowledge of AST levels in patients admitted for cocaine intoxication is a predictor of prognosis.

In the cases described, patients required a hospital stay longer than 15 days, reflecting greater susceptibility to adverse effects associated with the hospitalization period. In addition, they had complications in the days following admission, such as acute kidney injury, need for transfusions, and need for high doses of vasoactive drugs.

Studies have found that AST levels increased by up to 3-fold the upper limit of normal were associated with elevation in ALT and CPK. In the present study, there is a direct correlation between the increase in transaminases and the increase in CPK, and when associated with diffuse myalgia, it leads us to think of rhabdomyolysis as a differential diagnosis[13].

Rhabdomyolysis is a serious condition in which an insult causes muscle necrosis, leading to systemic release of intracellular content. In severe cases, rhabdomyolysis can cause acute kidney injury from leaked myoglobin, which is toxic to renal cells[4]. Rhabdomyolysis can be stratified into five etiological categories: physical (crush injury, trauma, burns, seizures), hypoxic (compartment syndrome, immobilization, vascular thrombosis), chemical (exogenous intoxications), biological (diabetic acidosis, insect stings, snake venom), and genetic[18].

Although there are no similar studies in the literature, cocaine use has been linked to the occurrence of rhabdomyolysis. Muscle damage can be potentiated by several factors, such as the direct myotoxic effect of the drug, vasoconstriction, ischemia, increased psychomotricity, and agitation.

A prospective study conducted with 39 chronic cocaine users at the University of Miami-Jackson Memorial Medical Center showed evidence consistent with rhabdomolysis in 20 patients that presented with diffuse myalgia and CPK levels more than 10-fold the upper limit of normal. Of the patients who developed rhabdomyolysis, 13 had some degree of renal dysfunction, with increased serum creatinine values, and 13 patients developed acute liver failure[19]. In addition, approximately 24% of cocaine users may have some degree of rhabdomyolysis, and many of these cases are not predictable from history or physical examination, making laboratory evaluation essential[20].

A retrospective study with 102 patients who were under intensive care at a tertiary care medical center showed the prevalence of severe acute hepatitis and cocaine abuse in 33% of the patients, and 11% of these had severe rhabdomyolysis[21].

The three patients reported in this study developed rhabdomyolysis from multiple causes - cocaine use, multiple trauma, psychomotor agitation - with CPK levels more than 10-fold the upper reference limit. In all of the cases described, patients evolved with acute kidney injury requiring dialysis, predicting a serious clinical situation.

In rhabdomyolysis, the increase in CPK levels peaks between 24 and 72 hours, and the half-life is approximately 36 hours. Commonly, CPK levels return to normal between 3 and 5 days after the injury[4]. In the reported cases, we observed that serum CPK levels remained elevated for more than ten days, showing a greater severity of the patients in our service.

Case reports suggest an association between neurological changes in rhabdomyolysis and chronic cocaine use. The changes described are delirium, psychosis, agitation, and low level of consciousness[11,22]. Of the patients presented, one had psychosis and two had disorientation. Psychosis secondary to rhabdomyolysis in cocaine users may increase the risk of muscle damage, leading to worsening of the clinical picture.

CONCLUSION

Despite the uncertainties of the pathophysiological mechanisms of hepatotoxicity secondary to cocaine use, cases such as those reported have been occurring more frequently. The association of rhabdomyolysis with severe acute hepatitis contributes to greater severity with high morbidity and mortality. In this context, the cases seem to confirm the assertion that all systems can be affected by cocaine toxicity, and suggest the importance of early diagnosis and an appropriate therapeutic approach. This is especially important because there is still no specific antidote for cocaine. The medical community should be aware of the possible complications of cocaine use and of the small difference between the recreational and toxic dose of cocaine.

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Participation of each member: *José Hícaro Hellano Gonçalves Lima Paiva* – Data collection and article preparation. *Vitória Nunes Medeiros* – Data collection and article preparation. *Ivelise Regina Canito Brasil* – Article review.

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