Significance of Alanine Aminotransferase Levels in Patients Admitted for Cocaine Intoxication

Fernanda Guollo, MD, Janaína L. Narciso-Schiavon, MD, PhD,* Adriana M. Barotto, MD,† Marlene Zannin, PhD,† and Leonardo L. Schiavon, MD, PhD**

Background: Experimental studies in animal models and case reports in humans have described the hepatotoxic potential of cocaine. However, there are few data regarding the clinical and laboratory characteristics of patients admitted for cocaine intoxication, particularly regarding the status of the liver enzymes.

Goal: To investigate the significance of alanine aminotransferase (ALT) levels in individuals hospitalized for acute cocaine intoxication.

Methods: Retrospective study with standardized chart review that included patients admitted between January 2003 and December 2010. Bivariate analyses were used to investigate factors associated with ALT above the upper tertile according to sex. Cases of marked ALT elevation were described in detail.

Results: Ninety-three patients were included (79% men, mean age of 27.73 ± 9.97 y). ALT above the upper tertile was associated with higher aspartate aminotransferase (AST), creatine phosphokinase, creatinine, and international normalized ratio. Higher levels of ALT were also related to acute renal failure and death. Five subjects had severe ALT elevation during follow-up and all had evidence of hepatocellular dysfunction (jaundice, prolonged prothrombin time with or without hepatic encephalopathy), rhabdomyolysis, and acute renal failure. AST/ALT ratio <2 was present in 2 subjects with severe ALT elevation at admission, but AST/ALT ratio >2 was observed in 3 cases with evidence of progression to acute liver injury.

Conclusions: In acute cocaine intoxication, higher ALT levels were associated with evidence of muscle damage, progression to acute renal failure, and death. Severe liver damage was observed in 5% of the sample and was associated with rhabdomyolysis and renal failure in all cases.

Key Words: cocaine, drug-induced liver injury, alanine aminotransferase, rhabdomyolysis

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Cocaine is a widely distributed drug, with variable penetration across the globe.[1] In 2007, the United Nations Office on Drugs and Crime estimated that 15.6 to 20.8 million people were cocaine users, which corresponds to nearly 0.5% of the world population between 15 and 64 years.[2] Despite the apparent decline in the use of cocaine observed in recent years in North America, other regions, such as South America, have shown a significant increase in the consumption.[2] Cocaine overdose is the leading cause of hospital visits associated with illegal drug use in the United States and is generally associated with the use of other drugs, primarily alcohol and tobacco.[3]

Cocaine is an indirect sympathomimetic agent, causing alterations in the central and peripheral nervous systems, primarily through blocking the dopamine transporter and serotonin and norepinephrine receptors.[4] This inhibition triggers an increase in the extracellular levels of dopamine, primarily in the dopaminergic compensation system.[5,6] This increase reduces the number of neurons required to receive stimuli and generate a reaction, increasing the sensitivity of the system.[7] Cocaine also inhibits voltage-gated sodium channels, generating local anesthetic effects.[8]

Cocaine is most commonly presented as hydrochloride salt and crack cocaine. Given its hydrosolubility, the hydrochloride salt can be used either intravenously or inhaled.[3,9] However, crack cocaine is a lower purity form of free-base cocaine, which is typically administered through the inhalation of the powdered substance as vaporized smoke.[10]

Acute cocaine intoxication has also been associated with potentially serious effects, such as myocardial ischemia, stroke, seizures, hyperthermia, and pulmonary edema.[11] The laboratory findings related to acute cocaine intoxication vary from slight creatine phosphokinase (CPK) and myoglobin increases, to electrolyte disturbances and life-threatening kidney failure observed in rhabdomyolysis.[3] There are few studies regarding the clinical and laboratory characteristics of patients admitted for cocaine intoxication, particularly regarding the status of the liver enzymes. Although experimental studies in animal models and case reports in humans have described the hepatotoxic potential of cocaine, aminotransferase elevations in acute cocaine intoxication are commonly attributed to muscular injury.[4,12,13] The aim of this study was to investigate the significance of alanine aminotransferase (ALT) levels in individuals admitted for acute cocaine intoxication.

METHODS

Patients

This retrospective cross sectional study was conducted using standardized patient records from the Center for Toxicological Information of Santa Catarina (CIT/SC) from January 2003 through December 2010. This center is a public facility that is highly regarded in the field of clinical

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From the *Division of Gastroenterology, Federal University of Santa Catarina, Florianópolis; and †Center for Toxicological Information of Santa Catarina (CIT/SC), SC, Brazil.

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Reprints: Leonardo L. Schiavon, MD, PhD, Depto Clínica Médica, Hospital Universitário, UFSC. R. Prof. Mª Flora Pausewang s/no, 3° andar, Trindade, 88040-900 Florianópolis, SC, Brasil (e-mail: leo-jf@uol.com.br).

toxicology and is located at the University Hospital of the Federal University of Santa Catarina (HU-UFSC).

The criterion for inclusion in the study was a diagnosis of cocaine intoxication as a reason for admission. The diagnosis of cocaine intoxication was based on medical history. Individuals with uncertain diagnosis and those without laboratory tests for ALT or CPK levels were excluded.

The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board.

Methods

Information concerning all the individuals admitted for cocaine intoxication was extracted from the standardized records. The following clinical variables were collected: age, sex, type of intoxication (intentional for recreational use, suicide attempt, or accidental), pattern of use, form of cocaine presentation (powder or crack), intoxications combined with other substances (alcohol, marijuana, ecstasy, Lysergic Acid Diethylamide, benzodiazepines, and opiates), mean arterial pressure and heart rate at admission, duration of hospital admission, presence of complications during the period of observation (psychomotor agitation that required benzodiazepines for control, seizures, stroke, chest pain, and acute renal failure), and death.

The following laboratory variables were studied (expressed in absolute values): aspartate aminotransferase (AST; reference range, 15 to 37 IU/L), ALT (reference range, 24 to 64 IU/L for men and 22 to 56 IU/L for women), total and direct bilirubin, platelet count, international normalized ratio (INR), CPK, creatinine, sodium, and potassium levels.

Habitual use of cocaine was defined as consumption with a frequency greater than once a month. Acute renal failure was defined as a creatinine rise of >0.5 mg/dL above the basal level (when available) or creatinine at admission >1.5 mg/dL.

Marked ALT elevation was considered as an increase >20 times the upper limit of normality. Additional data referring to the differential diagnosis with other causes of acute liver damage were revised in the cases meeting this criterion.

Statistical Analysis

The normality of the variable distribution was determined by the Kolmogorov-Smirnov test. The correlation between the numeric variables and the ALT levels was evaluated using Spearman correlation coefficient. Because of the significant impact of sex on the aminotransferase concentrations, the ALT levels were categorized in tertiles according to sex. The bivariate analysis of the factors associated with ALT higher than the upper tertile was conducted using Student t test or the Mann-Whitney test in the case of numeric variables and the χ^2 or Fisher exact tests in the case of categorical variables, as appropriate. A P value of <0.05 was considered statistically significant. All tests were 2-tailed and were performed by the SPSS software, version 17.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

Details regarding the clinical, demographic, and laboratory characteristics of the 93 included subjects are shown in Table 1. The mean age was 27.7 ± 10.0 years, and a male predominance was observed (78.7%). Intentional cocaine use was reported for 95.7% of the sample (93.6% recreational and 2.1% suicide attempt). The use of cocaine in the powder form was reported in 70.2% of the patients and the crack form was reported 29.8% of the individuals. Only one subject reported intravenous cocaine use. Mixed intoxication with alcohol was observed in 35.1% of the individuals, marijuana in 13.8%, Lysergic Acid Diethylamide in 1.1%, ecstasy in 1.1%, and benzodiazepines in 8.5% of the cases. No patient reported the use of opiates.

Factors Associated With the ALT Levels

The mean ALT level was 86.25 ± 191.05 IU/L (median of 36 IU/L). When evaluated using the Spearman correlation coefficient, the ALT levels were positively correlated with age ($r = 0.314$, $P = 0.002$), creatinine ($r = 0.347$, $P = 0.001$), AST ($r = 0.704$, $P < 0.001$), and CPK ($r = 0.319$, $P = 0.002$) levels. The ALT levels were not significantly correlated with the platelet count, sodium, and potassium levels.

The ALT levels were categorized in tertiles according to sex. Individuals with ALT above the upper tertile exhibited higher median creatinine (1.04 vs. 0.90 mg/dL; $P = 0.017$), CPK (1441.00 vs. 256.00 IU/L; $P = 0.010$), creatine phosphokinase MB fraction (29.0 vs. 8.0 IU/L, $P = 0.030$), AST (85.5 vs. 24.0 IU/L; $P < 0.001$), and INR (1.18 vs. 1.09; $P = 0.031$) values.

No associations were observed between ALT above the upper tertile and age, sex, form of drug presentation (powder or crack), intoxication mixed with alcohol,

TABLE 1. Demographic, Clinical, and Biochemical Characteristics of the Included Patients

Variables	Patients (n = 93)
Age (mean ± SD) (y)	27.73 ± 9.97
Male sex [n (%)]	74 (78.7)
Intentional cocaine use [n (%)]	90 (95.7)
Habitual user* [n (%)]	63 (96.9)
Form of cocaine presentation [n (%)]	
Powder	66 (70.2)
Crack	27 (29.8)
Mixed intoxication [n (%)]	
Alcohol	33 (35.1)
Marijuana	13 (13.8)
Ecstasy	1 (1.1)
LSD	1 (1.1)
Benzodiazepines	8 (8.5)
Opiate	0 (0)
MAP (mean ± SD) (mm Hg)	102.36 ± 17.98
Heart rate (mean ± SD) (bpm)	102.91 ± 28.40
ALT (median) (IU/L)	36.00
AST (median) (IU/L)	30.00
AST/ALT ratio	1.14 ± 0.69
CPK (median) (IU/L)	273.80
CPK-MB (median) (IU/L)†	10.00
Creatinine (median) (mg/dL)	0.95
Sodium (mean ± SD) (mEq/L)	138.84 ± 4.41
Potassium (median) (mEq/L)	3.90
INR (median)	1.11
Platelet count (median) (10^9/L)	236.00

Availability among included subjects: *65, †69 individuals.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase MB fraction; INR, international normalized ratio; LSD, Lysergic Acid Diethylamide; MAP, Mean arterial pressure.

benzodiazepines or marijuana, AST/ALT ratio, platelet count, sodium, and potassium (Table 2). In addition, median ALT levels were similar between habitual and occasional users (40.0 vs. 31.0 IU/L, $P = 0.480$).

Association Between ALT Levels and Complications

When the subjects were evaluated regarding the complications associated with acute cocaine intoxication, psychomotor agitation, requiring control through benzodiazepines, was observed in 43.0% of the subjects, seizures were observed in 10.6%, chest pain was observed in 8.5%, stroke in 2.1%, and acute renal failure was observed in 19.1% of the cases. Eight deaths (8.5%) were verified during the period of observation. The mean duration of hospitalization was 2.99 ± 5.35 days.

Compared with the other individuals, the patients with ALT above the upper tertile showed a higher prevalence of acute renal failure (34.4% vs. 9.8%; $P = 0.004$) and death during hospitalization (15.6% vs. 3.3%; $P = 0.045$). There was a trend toward higher proportion of patients requiring ≥ 4 days of hospitalization among those with higher ALT levels as compared with the others (34.4% vs. 18.0% days; $P = 0.078$). No significant differences were observed in the prevalence of psychomotor agitation, seizures, chest pain, or stroke when individuals with higher ALT were compared with the remaining subjects (Table 3).

TABLE 2. Factors Associated With Alanine Aminotransferase (ALT) Levels Above the Upper Tertile According to Sex (≥ 48 IU/L for Men and ≥ 36 IU/L For Women)

	ALT < Upper Tertile (n = 61)	ALT ≥ Upper Tertile (n = 32)	*P*
Age (mean ± SD) (y)	27.20 ± 11.62	28.58 ± 5.67	0.445
Male sex [n (%)]	48 (78.7)	25 (78.1)	0.950
Cocaine powder [n (%)]	41 (67.2)	24 (75.0)	0.437
Mixed intoxication [n (%)]			
Alcohol	24 (39.3)	9 (28.1)	0.283
Marijuana	8 (13.1)	5 (15.6)	0.760
Benzodiazepines	6 (9.8)	2 (6.3)	0.710
MAP (mean ± SD) (mm Hg)	105.17 ± 19.08	98.80 ± 16.22	0.218
Heart rate (mean ± SD) (bpm)	106.48 ± 29.12	97.86 ± 27.22	0.281
AST (median) (IU/L)	24.00	85.50	< 0.001
AST/ALT ratio	1.06 ± 0.61	1.31 ± 1.13	0.100
CPK (median) (IU/L)	256.00	1441.00	0.010
CPK-MB (median, IU/L)*	8.00	29.00	0.030
Creatinine (median) (mg/dL)	0.90	1.04	0.017
Sodium (mean ± DP) (mEq/L)	138.63 ± 4.32	139.08 ± 4.63	0.673
Potassium (median) (mEq/L)	3.8	4.0	0.120
INR (median)	1.09	1.18	0.031
Platelet count (median) (10^9/L)	233.50	245.00	0.535

*Available for 69 subjects.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase MB fraction; INR, international normalized ratio; MAP, mean arterial pressure.

Cases of Marked ALT Elevation Related to Cocaine Intoxication

Marked ALT elevation (> 20 times the upper limit) during hospitalization was observed in 5 individuals (Table 4). All patients were male, with a mean age of 31.2 ± 4.2 years. The individuals were admitted to the Intensive Care Unit and evidence of severe liver damage (jaundice and increased prothrombin time with or without hepatic encephalopathy) was observed in all cases. One of the individuals (case 3) exhibited hypotension, requiring vasoactive medication, and ultimately died from multiple organ failure; it was not possible to establish a reliable differential diagnosis with ischemic hepatitis in this case. No other obvious causes of acute liver damage were observed in the other individuals, despite extensive work-up (including blood tests for viral hepatitis and abdominal ultrasonography). Findings consistent with the diagnosis of hepatic encephalopathy were observed in 2 individuals (cases 1 and 2) without additional neurological findings suggestive of other specific central nervous system pathologies. All patients developed rhabdomyolysis and acute renal failure (2 patients required dialysis). An AST/ALT ratio < 2 was present in 2 individuals at admission. However, an AST/ALT ratio > 2 was observed in 3 cases with evidence of progression to acute liver damage.

DISCUSSION

Cocaine is a crystalline tropane alkaloid obtained from the leaves of *Erythroxylum coca*, a plant native from South America. After the isolation of cocaine in the mid-19th century, the substance was used medicinally, mainly as a local anesthetic; however, by the end of the 19th century, recreational cocaine use was also observed.[3] The significant popularization of cocaine as a drug of abuse occurred during the 20th century, and a significant increase in the consumption of this drug was observed throughout the world. Currently, cocaine intoxication is one of the main causes of admission to emergency services for drug use.[3]

The pharmacokinetics and bioavailability of cocaine depend on various factors, such as the form in which the drug is presented, the route of use, genetic factors, and the use of cocaine in conjunction with alcohol. Nearly half of the dose used undergoes hydrolysis and is converted into benzoylecgonine through carboxylesterase in the liver, as the main route for cocaine metabolism in humans.[14] A small portion of the cocaine absorbed undergoes hepatic *N*-demethylation, forming norcocaine, a metabolite that crosses the hematoencephalic barrier and produces clinical effects similar to the original compound.[14]

The physiopathology of the liver damage caused by cocaine is still not completely understood, although 2 main mechanisms have been suggested. The first mechanism involves the enzyme-catalyzed futile cycle between *N*-hydroxynorcocaine (a metabolite of norcocaine) and the amine oxide of norcocaine, which would deplete intracellular nicotinamide adenine dinucleotide phosphate, and reduce intrahepatic glutathione.[15] As a result, the cellular concentrations of hydrogen peroxide and radical superoxides generated through normal metabolism reach toxic levels, resulting in the lipid peroxidation of the cellular membranes.[15] The second proposed mechanism is based on the additional oxidation of norcocaine nitroxide into a highly reactive nitrosonium ion that would also deplete glutathione.[16]

TABLE 3. Prevalence of Complications During Hospitalization for Cocaine Intoxication and Its Relationship With ALT Levels Above the Upper Tertile (≥ 48 IU/L for Men and ≥ 36 IU/L for Women)

	All (n = 93)	ALT < Upper Tertile (n = 61)	ALT ≥ Upper Tertile (n = 32)	*P*
Duration of hospitalization ≥ 4 d [n (%)]	22 (23.7)	11 (18.0)	11 (34.4)	0.078
Psychomotor agitation* [n (%)]	40 (43.0)	27 (45.0)	13 (40.6)	0.687
Seizures [n (%)]	10 (10.6)	6 (9.8)	4 (12.5)	0.732
Chest pain [n (%)]	8 (8.5)	4 (6.6)	4 (12.5)	0.440
Stroke [n (%)]	2 (2.1)	0 (0)	2 (2.3)	0.116
Acute renal failure [n (%)]	18 (19.1)	6 (9.8)	11 (34.4)	0.004
Death [n (%)]	8 (8.5)	2 (3.3)	5 (15.6)	0.045

*Requiring benzodiazepines.
ALT indicates alanine aminotransferase.

The majority of studies evaluated the morphologic characteristics of liver damage caused by cocaine in animal models. In these studies, the pattern of the damage varied according to certain factors. In general, liver damage is more pronounced in the perivenular region (zone 3) in cases of high single doses. However, periportal damage (zone 1) was predominantly described in rats treated with smaller multiple doses of cocaine, those previously exposed to phenobarbital (an inducer of cytochrome P-450) or diethylmaleate (a glutathione depleter).[17] In humans, case series showed a trend for more intense damage in the perivenular region, confirming the findings of the animal models.[13,18]

Despite the evidence accumulated on the hepatotoxic potential of cocaine, there are little data concerning the significance of the ALT levels in patients admitted for cocaine intoxication, and until recently, the majority of studies involve reports and series of cases. In the present

TABLE 4. Clinical and Laboratory Characteristics, and Progression During the Hospitalization of Individuals With Marked Increase in Alanine Aminotransferase Levels (≥ 20 × the Upper Limit)

	Case 1	Case 2	Case 3	Case 4	Case 5
Clinical characteristics					
Sex	Male	Male	Male	Male	Male
Age	34	24	34	31	33
Habitual cocaine use*	Yes	Yes	Yes	Yes	Yes
Form of cocaine presentation	Powder	Powder	Powder	Powder	Powder
Mixed intoxication with alcohol	Yes	No	No	Yes	No
Hypotension at admission	No	No	Yes	No	No
Laboratory data at admission					
ALT (IU/L)	540	83	3244	39	164
AST (IU/L)	648	96	10267	81	409
AST/ALT ratio	1.2	1.15	3.16	2.07	2.49
CPK (IU/L)	2733	685	8160	1530	14576
Creatinine (mg/dL)	2.2	2.2	2.2	2.7	2.1
Bilirubin total (mg/dL)	5.59	0.27	4.9	1.02	0.46
Bilirubin direct (mg/dL)	4.78	0.06	1.2	0.54	0.14
INR	2.11	2.55	1.21	1.68	1.3
Laboratory data during hospitalization (minimum value − maximum value)					
ALT (IU/L)	540-3217	83-12835	277-5241	39-4371	164-9600
AST (IU/L)	138-1751	96-6260	310-2351	81-16205	59-11100
CPK (IU/L)	54-2733	685-8339	895-8160	1530-53049	496-48160
Creatinine (mg/dL)	1.0-2.2	1.4-2.9	2.2-10.2	2.6-10.5	1.7-3.2
Complications during treatment					
Psychomotor agitation	No	Yes	No	Yes	Yes
Seizures	No	No	Yes	No	Yes
Stroke	No	No	No	No	No
Chest pain	No	No	No	No	No
Acute renal failure	Yes	Yes	Yes	Yes	Yes
Need for dialysis	No	No	Yes	Yes	No
Hepatic encephalopathy	Yes	Yes	No	No	No
Jaundice	Yes	Yes	Yes	Yes	Yes
Prolonged prothrombin time	Yes	Yes	Yes	Yes	Yes
Death	No	No	Yes	No	No

*More than once a month.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; INR, international normalized ratio; MAP, mean arterial pressure; NA, not available.

study, ALT levels above the upper tertile were associated with higher AST and CPK levels. Although there are no similar studies in the literature, the use of cocaine has been related to the occurrence of rhabdomyolysis. Muscular damage, in these cases, can be induced through various factors, such as the direct myotoxic effect of the drug, vascular constriction and ischemia, increased physical activity (psychomotor agitation), and the presence of adulterants.[19] Even though ALT is typically considered a specific marker of liver damage, the skeletal muscles contain isozymes of CPK, AST, and ALT, which can be released through the blood flow in cases of muscular necrosis.[20] It is probable that the higher CPK levels observed among individuals with higher ALT reflect, at least in part, the liberation of ALT as a consequence of the muscular damage secondary to the effects of the drug. Nevertheless, this association could also indicate that higher ALT levels are associated with more serious forms of cocaine intoxication, leading to liver damage and rhabdomyolysis. In fact, in this study, individuals with higher ALT levels also have higher creatinine and INR at admission, also suggesting a relationship between the higher levels of hepatic enzymes and the severity of the condition.

Higher ALT levels were associated with the occurrence of acute renal failure and death during hospitalization. There was also a trend toward higher proportion of patients requiring ≥ 4 days of hospitalization among those with higher ALT levels as compared with the others. Only 1 previous report evaluated the relationship between the ALT levels and the occurrence of complications during hospitalization for cocaine intoxication, with similar findings to those obtained in the present study.[18] In this study, which included 39 patients with rhabdomyolysis secondary to cocaine abuse, individuals with ALT >400 IU/L showed an increased risk of complications, such as renal failure, disseminated intravascular coagulation, and death.[18] Curiously, even though in that study all the subjects had a diagnosis of rhabdomyolysis and the CPK levels did not differ among the groups, no patient with ALT < 400 IU/L developed renal failure, and only one of those with lower ALT died. These findings suggest that the knowledge of ALT levels in patients admitted for cocaine intoxication provides additional prognostic information, regardless of the presence of muscular damage.

Five individuals showed a marked ALT elevation (> 20 times the upper limit of normal) during treatment. In these cases, hepatocellular dysfunction and other complications, such as rhabdomyolysis and acute renal failure, were observed. Although a direct causal link cannot be completely established, the clinical context and exclusion of other common causes of liver failure suggest that the alterations observed in these cases are probably related to cocaine. The previous reports of cocaine hepatotoxicity in humans also corroborate the findings observed in this study and present several similarities, such as the occurrence of acute renal failure and rhabdomyolysis in nearly all the cases.[13,17,18,21,22]

As discussed above, the presence of rhabdomyolysis might be a complicating factor in the interpretation of the aminotransferase levels in cases of cocaine intoxication. The AST/ALT ratio has been used as an indicator of aminotransferase elevation associated with muscular damage, particularly in acute causes of rhabdomyolysis.[23] In the present study, the group with higher ALT levels presented AST/ALT ratios close to 1, suggesting little participation from muscular damage. However, 3 of the subjects who developed acute liver damage demonstrated AST/ALT ratio of >2 upon admission. These findings possibly reflect the strong association observed between rhabdomyolysis and liver damage, and suggest that the AST/ALT ratio is not a reliable marker for determining the cause of ALT elevation in this clinical context.

Some limitations of this study must be emphasized. The absence of systematic exclusion of other causes of ALT elevation might limit the interpretation of the results. However, from a practical point of view, this sample appears to reflect the peculiarities of those individuals in whom more specific tests results are usually not available at admission. It will be also of interest to evaluate the dynamic changes in ALT during hospitalization to identify specific evolutive patterns associated with complications and death. Even though the present study was not designed to address this issue, we believe that it may represent a start-point to prospective studies intended at investigating these questions in subjects admitted for cocaine intoxication. Another limitation is that the study design adopted and the absence of histologic data does not allow establishing the direct causal relationship between liver damage and cocaine. In fact, this question can only be addressed through prospective or experimental studies. Nevertheless, knowing the significance of ALT levels in patients admitted for cocaine intoxication might help to interpret this test, which is routinely used throughout the world.

It is possible to conclude that, in patients admitted for cocaine intoxication, higher ALT levels are associated with signs of muscular injury, progression to acute renal failure, and death. Despite the association observed between ALT and CPK levels, the low AST/ALT ratio among individuals with higher ALT levels indicates a hepatic cause as a probable source of this enzyme. In addition, severe liver damage was observed in 5% of the individuals and was associated with rhabdomyolysis and acute renal failure in all cases. Taken together, these data suggest that ALT levels in patients admitted for cocaine intoxication has prognostic value and can be used to identify individuals with higher risk for complications.

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