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Xenobiotic-Induced Rhabdomyolysis and its Relationship with Paraclinical Variables in Poisoned Patients

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Abstract

Background: Rhabdomyolysis is a clinical syndrome that occurs due to the damage to striated muscles after various conditions, one of the most common of which is drug poisoning. This study examined rhabdomyolysis in all types of poisoned hospitalized patients and its relationship with paraclinical variables, such as Creatine Phosphokinase (CPK) and the patients' level of creatinine, blood urea, and liver enzymes (alanine aminotransferase and aspartate aminotransferase).

Methods: A total of 105 patients suffering from rhabdomyolysis caused by poisoning were enrolled. The necessary information of the patients was extracted from their records, recorded in the research questionnaire, and analyzed using SPSS. Descriptive statistics indicators and Pearson's linear correlation coefficient were used for statistical analysis.

Results: The prevalence of rhabdomyolysis was 7.2%. Ninety-seven (92.4%) and 8 (7.6%) poisoned patients suffering from rhabdomyolysis were male and female, respectively. The most prevalent poisoning resulting in rhabdomyolysis was methadone poisoning (31.42%). There was a significantly positive correlation between CPK and urea, Cr, and AST; *i.e.*, by increasing CPK level, urea, Cr, and AST levels also increased, and by decreasing CPK level, urea, Cr, and AST levels also decreased. The incidence of an abnormal aminotransferase in the setting of rhabdomyolysis was high. In addition, the frequency of Acute Kidney Injury (AKI) ranged from 10.9 to over 16.9%.

Conclusion: Xenobiotics (*e.g.*, opioids, drugs, alcohol, and poisons), xenobiotic-induced coma, and/or xenobiotic-induced seizure are the causes of rhabdomyolysis in the present study. Briefly, the research findings revealed the highest prevalence of rhabdomyolysis in male youth poisoned by narcotics.

Keywords: Creatine kinase, Creatinine, Kidney, Liver, Rhabdomyolysis, Urea

Introduction

Poisoning occurs when materials interfere with the body's normal function after swallowing, inhalation, injection, or digestion of poisons, and causes serious consequences. The toxicity of available poisons and lack of medical services significantly increase the mortality due to self-poisoning in the tropics than in the industrialized world (1). One of the consequences of poisoning is rhabdomyolysis, a clinical syndrome that occurs due to the damage to striated muscles, myocytes, muscular fibers, and the release of intercellular elements into the bloodstream. Mechanisms causing this syndrome consist of damage to the cell wall, cellular hypoxia, and disorders in the sodium-potassium pump of muscle cells (2). This syndrome is caused by various factors, including the consumption of some medicines and poisons, surgery, trauma, malignant hyperthermia, muscular ischemia (crush syndrome, compartment syndrome, shock and coma, and arterial occlusive disease), high muscular stresses (marathon, status tension, dystonia, agitation, and delirium), impacting physical factors (high temperature, burns, *etc.*), viral and bacterial infections, metabolic and electrolyte disorders (hypokalemia, hyponatremia, hypernatremia, hypophosphatemia, and hypocalcemia), endocrine disorders (acute hyperglycemic crises, *hyper* aldosteronism, severe hyperthyroidism, hypothyroidism), genetic disorders, and neuropathies (3).

The most significant causes of rhabdomyolysis are crush syndrome, heavy physical exercises, alcohol, a large number of medicines, and poisons (4). The most prevalent symptoms of rhabdomyolysis are muscular pains, muscular dystrophy, and red-dark urine due to myoglobin. The most dangerous consequences of rhabdomyolysis are acute renal failure, life-threatening electrolyte disorders, and intravascular coagulation. Laboratory tests to diagnose rhabdomyolysis are Creatine Phosphokinase (CPK) with at least a fivefold increase compared with the normal level (CPK >1000) and/or myoglobin in urinary sediment or positive blood in urine analysis without hemoglobin in urinary sediment. Rhabdomyolysis diagnosis is not rejected based on negative myoglobin because the most effective paraclinical method for diagnosis is increased blood CPK level (5).

Some reports suggest that the levels of liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] also increase in rhabdomyolysis in addition to CPK (6,7). Clinical observations support this, but there is no consistent conclusion. Some authors believe that AST can be an indicator of muscle disease in the absence of hepatic injury (8,9), but others propose liver injury if AST and ALT levels increase (10).

Since rhabdomyolysis is observed in many patients, such as poisoned patients on the one hand and due to its dangerous and fatal consequences, on the other hand, this study aimed to examine rhabdomyolysis in all types of poisoned hospitalized patients and the relationship between the most common paraclinical factors (CPK) and the patients' level of AST, ALT, Creatinine (Cr), and blood urea.

Materials and Methods

Data collection, time, and place

In this retrospective cross-sectional study, the researchers reviewed the records of all the patients hospitalized for poisoning in 2015 and identified cases of rhabdomyolysis by referring to patients' records in Sina Hospital, affiliated to Tabriz University of Medical Sciences, Tabriz, Iran, a referral center for poisoned patients in the northwest of Iran. The patients' data, including gender, age, type of poison, and paraclinical findings, were extracted and recorded in datasheets.

Statistical analysis

The data were analyzed using SPSS 16. Descriptive statistics indices (severity of rhabdomyolysis relative to gender, age, and type of poison) and Pearson's linear correlational coefficient were used to evaluate the research findings. Quantitative data were expressed as means±SD, and qualitative data were expressed as frequencies and percentages. Statistical significance was set at $p<0.05$.

The inclusion and exclusion criteria

All the patients hospitalized due to poisoning and rhabdomyolysis were included in the study (inclusion criteria). Patients with a history of hepatic disease, chronic renal disease, viral infection, myocardial ischemia, recent trauma, hypotension with mean blood pressure <65 *mmHg* at initial hospital admission,

or non-xenobiotic induced rhabdomyolysis (*e.g.*, endocrine disorders, electrolyte disorders) were excluded from the study (exclusion criteria). The diagnosis of rhabdomyolysis was based on the history and CPK level >1000 *U/L*.

Ethical considerations

Ethical clearance was obtained from the Regional Ethics Committee (Islamic Azad University 1392: 93860524183 and 1392:93850550797). Also, the patients' information remained confidential in this study.

Results

The total of poisoned patients hospitalized in Sina Hospital in 2015 was 1450 cases. Only in 4 patients, the possibility of concomitant acute hepatic injury and rhabdomyolysis was suggested. After excluding some patients, 105 patients (7.2%) suffered from rhabdomyolysis caused by poisoning (CPK >1000). Among them, 82 patients had a decreased level of consciousness, 14 had a body temperature >38ºC due to aspiration pneumonia, and 14 had tramadol-induced seizures.

The liver ultrasound examinations of all the patients with elevated hepatic enzymes were normal. Hospital admission time between patients based on ingested xenobiotic type, signs, symptoms and complications were different.

The extent of rhabdomyolysis resulting from poisoning concerning gender and age

Thirty-two (30.5%), 22 (21%), 14 (13.3%), and 35 (37.5%) patients were admitted in spring, summer, autumn, and winter, respectively. Ninety-seven (92.4%) and 8 (7.6%) of the poisoned patients suffering from rhabdomyolysis were male and female, respectively (Table 1). There were no significant differences between the levels of CPK, Urea, Cr, LDH, AST, and ALT between the two genders (p>0.05). The mean ages of all the poisoned patients and those with rhabdomyolysis were 28.62±14.22 *yr* and 39.39±15.31 yr, respectively, with 39.61±15.58 *yr* and 36.75±12.10 *yr* for males and females,

Table 1. Mean and standard deviation of CPK, Urea, Cr, LDH, AST, and ALT in the studied patients

Lab parameters	Arrival time Mean ± SD (N)		During hospital admission Mean ± SD (N)		At discharge Mean ± SD (N)	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CPK	3973.98±5163.06 (62)		4283.75±4949.38 (90)		2979.95±8312.23 (68)	
	68	25269	142	24183	64	49200
AST	138.77±149.62 (72)		133.06±117.04 (66)		83.08±112.72 (48)	
	19	638	12	720	12	700
ALT	88.94±113.52 (73)		105.53±127.77 (66)		93.56±114.80 (48)	
	13	569	13	711	10	712
Urea	50.37±46.60 (83)		42.37±44.68 (77)		39.98±43.88 (64)	
	13	280	15	250	14	305
Cr	1.51±1.42 (83)		1.38±1.46 (77)		1.35±1.67 (64)	
	0.5	8.5	0.5	8.5	0.5	9.7
LDH*	670.22±407.48 (9)		2669.23±6442.21 (13)		553.71±144.10 (7)	
	288	1560	418	24080	367	788

* LDH: Lactate Dehydrogenase.

respectively. Figure 1 presents the age distribution of the studied patients. Three age groups exhibited the highest rhabdomyolysis prevalence:

The age group of 16-25 years, including 23 patients (21.9%): The most significant poisoning cause was tramadol (10 patients, 43.4%). The total number of poisoned patients was 521 (35.93%).

The age group of 26-35 years, including 26 patients (24.7%): The most significant poisoning cause was methadone. The total number of poisoned patients was 609 (42%).

The age group of 36-45 years, including 25 patients (23.8%): The most significant poisoning cause was methadone (10 patients, 40%). The total number of poisoned patients was 120 (8.27%).

The most prevalent poisoning to causes rhabdomyolysis was methadone (33 cases, 31.4%, including 32 males and one female). 97 male patients were poisoned with methadone (32 cases with a mean age of 40.62±10.96), opium/heroin/morphine (21 cases with a mean age of 43.90±16.61), tramadol (17 cases with a mean age of 28.82±13.96), alcohol (5 cases with a mean age of 38.80±14.53), carbon monoxide (4 cases with a mean age of 36.75±10.04), and others (18 cases with a mean age of 43.83±20.34), including benzodiazepines, antidepressants, insecticides, herbicides, and rodenticides, respectively. Also, eight female patients were poisoned with benzodiazepines (three cases aged 30, 35, and 40), antidepressants (two cases aged 36 and 54), carbon monoxide (one case aged 17 years old), rodenticides (one case aged 52), and methadone (one case aged 30).

The incidence of an abnormal AST (>40 *IU/L*) in the setting of rhabdomyolysis (CPK >1,000 *IU/L*) was 77.8, 83.3, and 56.2% at arrival time, time of hospitalization, and at discharge, respectively. Also, the incidence of an abnormal ALT (>40 *IU/L*) in the setting of rhabdomyolysis was 53.4, 60.6, and 56.2% at arrival time, time of hospitalization, and at discharge, respectively.

Relationship between CPK and other laboratory parameters of the patients

The patients were evaluated by taking three steps and performing Pearson's correlation test (level of significance=0.05). The results are shown in table 2. Liver enzymes were also elevated in the patients with elevated CPK levels. There was no significant relationship between CPK and ALT levels (p>0.05). However, the relationship between the CPK and AST levels was statistically significant.

Arrival time

There was a significantly positive correlation between CPK and urea, Cr, AST; *i.e.*, with an increase in CPK levels, urea, Cr, and AST levels increased, too.

During hospitalization (admission-discharge)

There was a significantly positive correlation between CPK and urea, Cr, AST; *i.e.*, with an increase in CPK

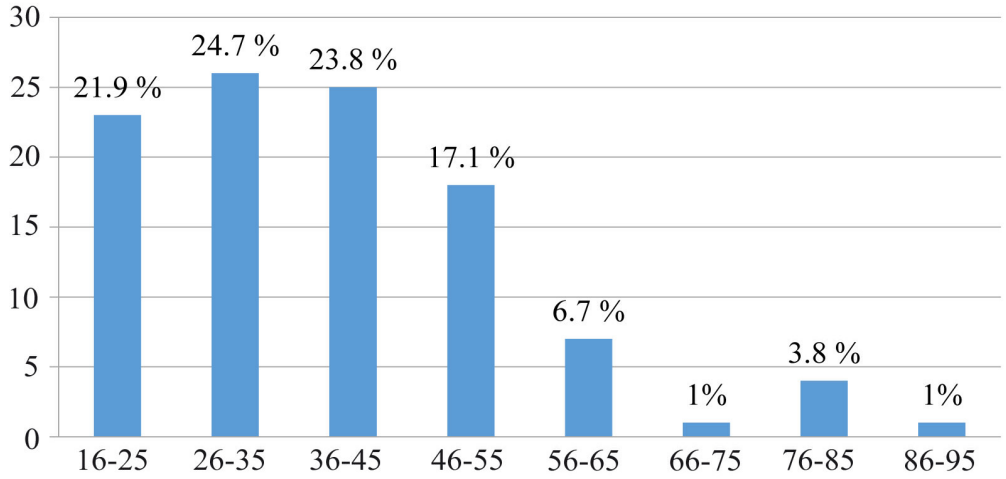

Figure 1. Age distribution of the studied patients (Min:16 yr; Max: 90 yr).

Table 2. Correlations between CPK and other lab parameters

			Urea	Creatinine	AST	ALT
CPK	Arrival time	Correlations	Yes	Yes	Yes	No
		p-value	0.007	0.002	0.037	
		Pearson correlation	+0.355	+0.404	+0.275	p=0.152
		R Sq linear	0.126	0.163	0.075	
	During hospital admission	Correlations	Yes	Yes	Yes	No
		p-value	0.004	0.021	0.006	
		Pearson correlation	+0.332	+0.266	+0.344	p=0.112
		R Sq linear	0.112	0.071	0.118	
	At the discharge time	Correlations	Yes	Yes	Yes	No
		p-value	<0.0001	<0.0001	<0.0001	
		Pearson correlation	+0.711	+0.828	+0.659	p=0.717
		R Sq linear	0.506	0.685	0.434	

level, urea, Cr, and AST levels increased, and with a decrease in CPK level, urea, Cr, and AST levels decreased.

Discharge

There was a significantly positive correlation between CPK and urea, Cr, AST levels; *i.e.*, with a decrease in CPK levels, urea, Cr, and AST levels decreased.

Acute kidney injury (AKI, acute renal failure)

In this study, the frequency of AKI ranged from 10.9 to over 16.9 percent: at discharge (or death) (10.9%), during hospitalization (16.9 %), and arrival time (16.9%). There was a significantly positive correlation between age and Cr; *i.e.*, by aging, only Cr levels also increased at arrival time (Pearson's correlation: +0.248, p=0.024). There was a significantly positive correlation between CPK and Cr, *i.e.*, with an increase in CPK level, Cr levels increased, too, and with a decrease in CPK levels, Cr levels decreased, too (Table 2). In CPK levels >2000, the risk of AKI (Cr>1.5) increased 2.33 folds.

Mortality

Nine men and one female patient (with a mean age 46.30±18.19) had died due to the severity of poisoning and/or its complications, and 95 (with a mean age 38.66±14.90) had survived. The mean (SD) of CPK, Cr, and urea levels were higher in deceased patients, with a statistical relationship only between urea and creatinine during hospital admission, as there was an increase in mortality rate with an increase in Cr and urea levels. Table 3 presents the results.

Discussion

One of the most prevalent consequences of acute poisoning with alcohol, narcotics, and psychotropic medicines is rhabdomyolysis, resulting in ARF and even death. Therefore, it should be diagnosed early to decrease the complications. Today, this clinical syndrome is one of the main causes of Acute Renal Failure (ARF), with an incidence of 4-51% (4,11,12) in previous studies and 10.9–16.9% in the present study. Although most international studies view ethanol poisoning as one of the main causes of rhabdomyolysis, it does not significantly impact the subject of this research and some other Iranian studies. This study and studies by Taheri *et al* (13) and Mousavi *et al* (14) showed 5.7, 7.3, and 2.5% roles for alcohol, respectively, since it is possible that Iranians are not inclined toward ethanol consumption due to religious beliefs and the inaccessibility of standard ethanol.

Table 3. Mean and standard deviation of CPK, Urea, Cr, in alive and dead patients

Lab parameters	Arrival time		During hospital admission		At discharge	
	Alive/dead	p-value	Alive/dead	p-value	Alive/dead	p-value
CPK	3867.77±5146.64 (58) 5979.75±6381.06 (4)	0.302	3672.59±4243.12 (83) 10159.85±8592.24 (7)	0.093	2375.98±6288.13 (63) 10590.00±21593.88 (5)	0.444
Urea	47.33±44.91 (75) 80.25±57.09 (8)	0.221	34.21±31.68 (69) 112.75±74.88 (8)	0.021	30.84±20.42 (58) 128.33±95.78 (6)	0.055
Cr	1.34±1.25 (75) 3.05± -2.10 (8)	0.055	1.07±0.82 (69) 4.10±2.67 (8)	0.015	1.02±0.88 (58) 4.49±3.68 (6)	0.069

In addition, due to legal and religious limitations, ethanol drinkers refer to hospitals at a lower rate and deny ethanol consumption during hospitalization.

A small number of studies have investigated rhabdomyolysis by using large sample sizes for a long time. The total number of poisoned patients being hospitalized was 1450. Specifically, 105 patients (7.2%) suffered from rhabdomyolysis caused by poisoning (CPK >1000). Taheri *et al* examined patients poisoned by forbidden and illegal materials (narcotics, alcohol, and psychotropic agents) in six months. They studied 82 patients, 26.8% of whom suffered from rhabdomyolysis (13). Moosavi *et al* focused on acute poisoning in 7339 patients of Loghman Hospital in six months, 450 of whom were treated in ICU (14), with 36.6% suffering from rhabdomyolysis. Similarly, the majority of patients in these studies were male (13-15). Also, consistent with the present study, the most significant causes of rhabdomyolysis in Iranian toxicology wards are opioids (13-15).

This detailed study consisted of a 1-year observation of all the patients hospitalized with a diagnosis of poisoning. Accordingly, rhabdomyolysis prevalence can be analyzed more precisely with more remarkable similarity to the population at large. Moreover, all typologies of poisoning are covered. The most prevalent causes were methadone, other opioids such as opium, heroin, morphine, and tramadol, and alcohol and carbon monoxide. This research examined the relationship between CPK and urea, creatinine AST, and ALT, in association with the analysis of the prevalence of rhabdomyolysis in terms of age, gender, and the type of poison. There was a significant positive correlation between CPK and urea, Cr, and AST, *i.e.*, an increase in CPK level was associated with an increase in urea, Cr, and AST levels, and a decrease in CPK levels was associated with a decrease in urea, Cr, and AST levels. Therefore, rhabdomyolysis should be diagnosed early and treated during hospitalization to decrease its morbidity and mortality.

Our findings revealed that nonspecific liver function tests could increase in rhabdomyolysis. In the present study, we found a significant relationship between serum levels of CPK and AST. Pertusi *et al* believe that the rise in ALT level might be due to muscle or hepatic injuries. They recommended more specific tests, such as GGT (gamma-glutamyl transferase), to evaluate liver injuries (10). Bhagwat attributed the rise in AST and ALT to rhabdomyolysis rather than hepatic injuries in snake bites (16). Malinoski advocated muscle injuries rather than hepatic injuries to interpret the rise in AST, too (17). Eizadi-Mood *et al* stated that the rise in ALT and CPK could be due to muscle injuries if the hepatic disease is ruled out (18). Other studies suggest that aminotransferase abnormalities, particularly AST, are common in rhabdomyolysis (19-21). AST concentrations decrease parallel to CPK, suggesting that skeletal muscle might be a significant source of AST elevation in these patients, and hepatic dysfunction is not a complication of rhabdomyolysis or liver failure is not a concurrent disease with rhabdomyolysis.

However, considering the theory of hypoxia for the pathogenesis of muscle injuries and rhabdomyolysis in poisoning cases, the same mechanism might lead to hypoxic liver injury and an increase in liver enzymes concurrently. Therefore, evaluation of such patients for concomitant liver injury is recommended. If there is a suspicion of liver failure, the recommended diagnostic method is to take a medical history and evaluate serum GGT levels (22).

Conclusion

Xenobiotics (*e.g.*, opioids, drugs, alcohol, and poisons), xenobiotic-induced coma, and/or xenobiotic-induced seizures were the causes of rhabdomyolysis in the present study. Briefly, the research findings revealed the highest prevalence of rhabdomyolysis in male youth poisoned by narcotics. This research indicates drug misuse youth as active labor forces and subsequently one of the severe social crises that the authorities should monitor and control. Typical clinical symptoms and rhabdomyolysis symptoms do not occur at the same time. Hence, proper clinical workouts and timely para-clinical tests play a significant role in the initial diagnosis and timely treatment to avoid ARF.

Compliance with ethical guidelines

Ethical clearance was obtained from the Regional Ethics Committee (Islamic Azad University 1392: 93860524183 and 1392:93850550797). Also, the patients' information remained confidential in this study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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