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Incidence, Etiology, and Outcomes of Rhabdomyolysis in a Single Tertiary Referral Center

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We have encountered numerous cases of rhabdomyolysis associated with acute pesticide intoxication; however, the cause, incidence, and treatment outcomes of rhabdomyolysis have not been studied. The current study involved 2,125 patients hospitalized with acute chemical poisoning. Based on clinical and laboratory parameters and treatment outcomes, we found that overall incidence of rhabdomyolysis in our hospital was 0.06% (93 of 143,830 patients admitted), but the incidence associated with acute pesticide intoxication was 1.8% (33 of 1,793 cases). The incidence of rhabdomyolysis after pesticide intoxication was significantly higher in men than in women ($P = 0.010$). The amount of pesticide ingested was significantly higher in rhabdomyolysis patients than that in those who did not develop rhabdomyolysis (mean ± SD, 114.1 ± 79.5 mL vs 74.1 ± 94.2 mL, $P = 0.010$). Our results show that pesticide intoxication is a frequent cause of rhabdomyolysis and is more common among men than women. The volume of pesticide ingested, and not the degree of human toxicity, is the main factor influencing the incidence of rhabdomyolysis.

Key Words: Acute Kidney Injury; Intoxication; Pesticides; Rhabdomyolysis; Surfactant

INTRODUCTION

Various causes of rhabdomyolysis have been described, such as exertion, crush injuries, ischemia, metabolic disorders, abnormal body temperatures, infection, autoimmune muscle damage, and drugs and/or toxins (1). Among the drugs known to induce rhabdomyolysis, the most common examples are statins (2) and fibrates (3). Antipsychotic medications (4) and neuromuscular blocking agents (5) are also known to cause rhabdomyolysis. In addition, substance abuse (6, 7) including alcohol, amphetamine, cocaine, heroin, and ketamine may induce the condition. Poisons linked to rhabdomyolysis include heavy metals (8) and venoms from insects or snakes (9, 10).

Acute pesticide intoxication, a method commonly used by people commiting suicide, is unique in that a specific toxic substance may be associated with the development of rhabdomyolysis (11-14). We have encountered many patients with rhabdomyolysis associated with acute pesticide intoxication at our hospital, accounting for approximately 500 cases per year (15, 16). The current study was designed to assess the etiology, incidence, and treatment outcomes of rhabdomyolysis at our hospital over a 5-yr period.

MATERIALS AND METHODS

Study design and data collection

This cross-sectional study was performed by reviewing the medical records of rhabdomyolysis patients admitted to the Department of Nephrotoxicology, Soonchunhyang Cheonan Hospital, Korea, between July 2006 and June 2011 (Fig. 1). The parent population included all patients admitted during the investigation period. We screened patients with rhabdomyolysis on the basis of the current consensus definition of rhabdomyolysis (creatine kinase [CK] level higher than 1,000 U/L), using an order communication system and electronic medical records. We documented patient age, sex, hospitalization period, the amount of pesticide ingested, the active toxic compounds, the time lag to hospital admission, and laboratory findings. We also scored acute renal failure (ARF) and mortality to assess the complications and outcomes of rhabdomyolysis.

Definition of ARF

ARF was diagnosed according to the Risk, Injury, Failure, Loss, and End-Stage Renal Disease criteria for ARF (17). In brief, ARF was diagnosed when the serum creatinine level increased 3

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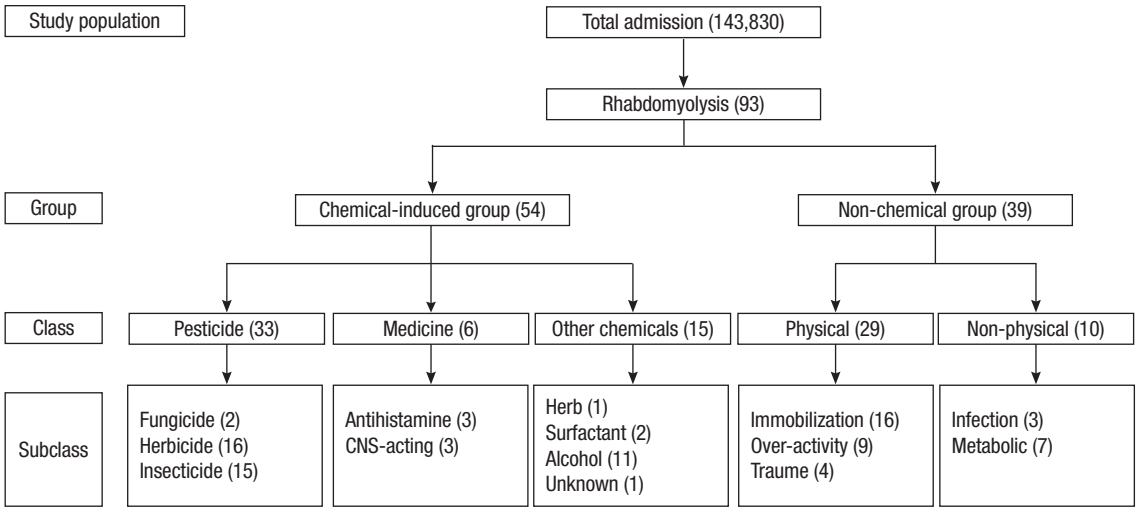

Fig. 1. Causes of rhabdomyolysis in the current study. The numbers of cases are shown in parentheses. CNS, central nervous system.

times that of the lowest level during the observation period retrospectively, when the glomerular filtration rate decreased > 75% of the lowest level during the admission, when the serum creatinine level increased over 4 mg/dL without a history of renal disease, when there was an acute rise of serum creatinine ≥ 0.5 mg/dL, and when the urine output decreased to < 0.3 mL/[kg·h], or if anuria persisted for > 12 hr.

Causes of rhabdomyolysis

Patients were divided into 2 groups based on the cause of rhabdomyolysis (the chemical-induced group and the non-chemical group). The chemical-induced group was further divided into 3 classes based on the type of chemical agent (pesticide, medicine, and other chemicals) (Fig. 1). The pesticide class was further divided into 3 subclasses (fungicides, herbicides, and insecticides). The medicine class, which included cases of acute overdose rather than actual intoxication, was categorized into 5 subclasses according to the World Health Organization Anatomical Therapeutic Chemical Classification System, as follows: analgesics (N02 and M01), antihistamines (D04), central nervous system (CNS)–acting agents (N03, N05, and N06), mixed medications, and others. For all pesticides, the amount ingested was estimated based on the number of swallows (1 mouthful was equivalent to 20 mL). The non-chemical group was categorized into physical and non-physical subclasses (Fig. 1).

Statistical analysis

Continuous variables are shown as the mean ± SD, with or without the median value and range, and categorical variables are shown as the frequency (the number of cases and percentage). The differences between groups were analyzed using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. To analyze the differences among > 3 groups, we used the Kruskal-Wallis test. Statistical analyses were performed using SPSS software, version 14.0 (SPSS, Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant. Because of the limited sample size, laboratory measurements of muscle enzyme levels were compared among the pesticide, chemical (other than pesticide), and physical classes.

Ethics statement

The study protocol and design were reviewed and approved by the institutional review board (IRB) of Soonchunhyang University Cheonan Hospital (IRB approval number: 2013-38). Informed consent was not obtained because of retrospective design of the study.

RESULTS

The overall incidence of rhabdomyolysis in our hospital was 0.06% (93 cases of 143,830 total admissions) (Fig. 1), whereas the incidence of rhabdomyolysis in patients with acute pesticide intoxication was much higher (1.8% [33 of 1,793 cases]) (Table 1). The frequency of rhabdomyolysis caused by different active ingredients varied (Tables 2 and 3). Not all pesticides that may cause severe human toxicity triggered rhabdomyolysis. For example, among the 1,420 patients with acute paraquat intoxication, none had rhabdomyolysis. In contrast, the frequency of rhabdomyolysis was high in patients poisoned with certain pesticides, as shown in Table 3.

The incidence of rhabdomyolysis associated with pesticides was significantly higher among men than that among women (Table 4). However, this sex difference was not observed for the other classes of chemicals. The amount of pesticide ingested was significantly higher among rhabdomyolysis patients than among non-rhabdomyolysis patients (mean ± SD, 114.1 ± 79.5 mL vs 74.1 ± 94.2 mL, *P* = 0.010); however, among the rhabdo-

Table 1. Demographic characteristics of patients in the chemical-induced group

Class of chemicals	Cases (No.)*	Subclass	Cases (No.)*	Mean age (yr)	Sex (M/F)
Pesticide	33/1,793	Paraquat	0/1,420	51.0	852/568
		Fungicide	2/16	45.5	8/8
		Herbicide	16/182	50.6	111/71
		Insecticide	15/123	52.2	80/43
		Mixed-pesticide	0/42	52.9	26/16
		Others	0/2	48.0	2/0
		Unknown	0/8	49.0	4/4
Medicine†	6/224	Analgesics	0/11	29.0	1/10
		Antihistamine	3/34	32.6	7/27
		CNS-acting	3/110	45.9	29/81
		Mixed medicine	0/56	39.1	8/48
		Others	0/13	51.8	3/10
Other chemicals	15/108	Acid	0/8	56.4	2/6
		Alkali	0/20	39.0	5/15
		Others	0/12	42.6	7/5
		Surfactant	2/28	52.4	15/13
		Alcohol	11/11	48.7	10/1
		Herbal drug	1/6	57.5	1/5
		Rodenticide	0/5	43.2	3/2
		Mixed	0/7	50.1	2/5
		Others	0/2	40.0	2/0
		Unknown	1/9	59.1	5/4
Total	54/2,125			51.2	1,183/942

*The number of rhabdomyolysis patients and total admitted patients; †The medicine class was categorized into 5 subclasses according to the World Health Organization Anatomical Therapeutic Chemical Classification System: analgesics (N02 and M01), antihistamines (D04), CNS-acting agents (N03, N05, and N06), mixed medications, and others. M, male; F, female; CNS, central nervous system.

Table 2. Details of active ingredients causing rhabdomyolysis for each class in the chemical-induced group

Pesticides (n = 33)	Medicines (n = 6)	Other chemicals (n = 15)
Fungicides (n = 2)	Antihistamine (n = 3)	Herbal drug (n = 1)
Mixture of carpropamid and edifenphos	Doxylamine (n = 2)	Wild mushroom
Tebuconazole	Diphenhydramine (n = 1)	Surfactant (n = 2)
Herbicides (n = 16)	CNS-acting drug (n = 3)	Polyoxyethylene arylalkyl ethylene
Alachlor (n = 1)	Combination of mirtazapine, venrafaxine, perphenazine, diazepam, and zolpidem	Mixture of alkylaryl polyethoxylate and sodium salt of alkylsulfonated alkylate
Dicamba (n = 3)	Combination of risperidone, quetiapine, haloperidol, and lorazepam	Alcohol (n = 11)
Glyphosate (n = 6)	Unknown CNS-acting drug	Ethanol (n = 11)
Glufosinate (n = 6)		Unknown (n = 1)
Insecticides (n = 15)		
DDVP (n = 3)		
Acetamiprid (n = 2)		
Lufenurone (n = 1)		
Chlorpyrifos (n = 1)		
Diazinon (n = 1)		
BPMC (n = 1)		
Fenitrothion (n = 1)		
Phosphamidon (n = 1)		
Propamocarb (n = 1)		
Mixture of cypermethrin and chlorpyrifos (n = 1)		
Mixture of cypermethrin, DDVP, and diazinon (n = 1)		
Mixture of DDVP, acetamiprid, and buprofezin (n = 1)		

DDVP, dichlorvos or 2,2-dichlorovinyl dimethyl phosphate; BPMC, fenobucarb; CNS, central nervous system.

Table 3. Frequency of rhabdomyolysis and WHO toxicity of pesticides

Frequency	Active toxic compound	Cases (No)*	WHO toxicity†
High	Tebuconazole	1/1	III
	Mixture of carpropamid and edifenphos	1/1	U and Ib
	Acetamiprid	2/2	NC‡
	Lufenurone	1/1	III
	Propamocarb	1/1	U
	Mixture of cypermethrin and chlorpyrifos	1/1	II and II
	Mixture of cypermethrin, DDVP, and diazinon	1/1	II and II
	Mixture of DDVP, acetamiprid, and buprofezin	1/1	Ib, NC§, U
	DDVP	3/5	Ib
	BPMC	1/2	II
Moderate	Chlorpyrifos	1/3	II
	Phosphamidon	1/3	Ia
	Dicamba	3/11	III
	Diazinon	1/4	II
	Fenitrothion	1/5	II
Low	Glufosinate	6/46	III
	Glyphosate	6/77	U
	Alachlor	1/13	III
	Paraquat	0/1,420	II

*The number of rhabdomyolysis patients and total patients in each subclass; †WHO toxicity classes; ‡Not classified; §WHO toxicity class of acetamiprid is currently "not classified." However, the acute oral LD50 for male rats is 217 mg/kg. WHO, World Health Organization; DDVP, dichlorvos or 2,2-dichlorovinyl dimethyl phosphate; BPMC, fenobucarb; Ia, extremely hazardous; Ib, highly hazardous; II, moderately hazardous; III, slightly hazardous; U, unlikely to present acute hazard in normal use.

Table 4. Age, sex, time lag to hospital admission, amount of ingestion, and alcohol coingestion of patients in the pesticide class

Parameters	Rhabdomyolysis (n = 33)	No rhabdomyolysis (n = 1,760)	*P*
Age (yr)			
Mean ± SD	53.7 ± 14.7	50.9 ± 16.2	0.31
Sex (male/female)	28/5	204/136	0.01
Amount of ingestion (mL)			
Mean ± SD	114.1 ± 79.5	74.1 ± 94.2	0.01
Median	100	40	
Range	20-300	1-650	
Time to hospital (hr)			
Mean ± SD	17.5 ± 39.0	8.4 ± 31.5	0.14
Median	3.5	5.0	
Range	0.5-168.0	0.2-480.0	
Alcohol ingestion (Yes/No)	15/18	141/199	0.70
Serum alcohol concentration (mg/dL)			
Mean ± SD	25.5 ± 66.5	49.2 ± 75.1	0.08
Median	2.4	2.8	
Range	1.0-190	1.0-243.0	

myolysis and non-rhabdomyolysis patients who ingested pesticides, there were no differences in age, time lag to hospital admission, or the incidence of alcohol coingestion.

There was no difference in the incidence of ARF or mortality between the chemical-induced group and the non-chemical group. A binary logistic regression analysis showed that the risk factor most closely associated with ARF was the peak level of serum myoglobin ($P = 0.04$), but the odds ratio (1.001) was not significant; none of the examined risk factors was significantly associated with mortality.

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Table 5. ARF incidence, hospitalization duration, and peak laboratory parameters of patients in the pesticide, chemical other than pesticide, and physical classes

Peak value*	Pesticide (n = 33)	Chemical other than pesticide (n = 21)	Physical (n = 29)	*P*
ARF (incidence %)	33.3	33.3	41.3	0.80
Mortality (%)	12.1	4.8	10.3	0.70
Hospitalization (days)				
Mean ± SD	18. 8 ± 35.8	10.9 ± 5.1	10.4 ± 5.4	0.90
Median	9	11	9	
Range	3-204	2-21	4-22	
Creatine kinase (U/L)				
Mean ± SD	5,677 ± 7,364	22,377 ± 37,357	14,912 ± 20,057	0.01
Median	2,738	8,220	7,032	
Range	904-35,600	1,294-153,900	1,019-85,440	
Myoglobin (μg/L)	1,461 ± 1135	2,163 ± 1186	2,208 ± 105	0.02
LDH (U/L)				
Mean ± SD	73.1 ± 165.4	84.2 ± 89.1	65.9 ± 51.7	0.10
Median	38.1	63.6	42.5	
Range	15.8-987.8	23.0-447.7	13.2-214.5	
Uric acid (mg/dL)	6.8 ± 2.7	8.4 ± 3.8	7.2 ± 3.3	0.20
Phosphorus (mg/dL)	4.6 ± 2.5	5.3 ± 3.4	4.0 ± 1.2	0.30
AST (U/L)				
Mean ± SD	483 ± 1,822	891 ± 2,837	341 ± 448	0.30
Median	117	200	186	
Range	32-10,600	24-13,200	35-1,668	
ALT (U/L)				
Mean ± SD	198 ± 686	362 ± 1,114	115.6 ± 89.0	0.30
Median	62	103	81	
Range	24-4,010	10-5,190	26-308	
Potassium (mEq/L)	4.6 ± 0.6	4.4 ± 1.1	4.5 ± 0.6	0.80
Creatinine (mg/dL)				
Mean ± SD	1.6 ± 1.4	1.9 ± 2.0	1.7 ± 1.2	0.80
Median	1.1	1.0	1.2	
Range	0.5-6.6	0.5-7.2	0.6-5.0	
Urea nitrogen (mM/L)	26.3 ± 15.1	32.5 ± 30.8	30.0 ± 20.2	0.60
Urine specific gravity	1.015 ± 0.007	1.016 ± 0.006	1.019 ± 0.008	0.20

Note: Continuous variables expressed as mean ± SD, median, or range. Conversion factors for units: myoglobin in μg/L to mM/L, × 0.0571; uric acid in mg/dL to μM/L, × 59.48; phosphorus in mg/dL to mM/L, × 0.3229; potassium in mEq/L to mM/L, × 1.0; creatinine in mg/dL to μM/L, × 88.4; urea nitrogen in mg/dL to mM/L, × 0.357.
*The highest value anytime during the measured data that was higher than the upper limit. ARF, acute kidney injury; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Peak CK levels were significantly lower in the pesticide class than those in the non-pesticide chemical classes ($P = 0.01$) or those in the physical class ($P = 0.01$). Peak serum myoglobin levels in the pesticide class were also lower than those in the physical class ($P = 0.01$) (Table 5).

In the herbicide subclass, all 16 rhabdomyolysis patients were men, showing a sex difference in the incidence of rhabdomyolysis. The amount of chemical ingested was significantly higher for the rhabdomyolysis patients than for the non-rhabdomyolysis patients ($P = 0.01$, data not shown). The time lag to hospital admission was significantly shorter ($P = 0.02$, data not shown) for the rhabdomyolysis patients than for the non-rhabdomyolysis patients.

Among the 224 patients in the medicine class, rhabdomyolysis developed only in the antihistamine and CNS-acting drug subclasses (Tables 1 and 2 and Fig. 1). During the 5-yr observational period, 8,486,084 tablets of 5 types of statin were prescribed to 27,902 patients. The hydroxymethylglutaryl-coenzyme A reductase inhibitor statin did not result in rhabdomyolysis in our study. Two patients were admitted to our hospital during the observational period, not because of rhabdomyolysis but for observation after statin overdose. Two of the 28 patients with acute surfactant intoxication had rhabdomyolysis (Tables 1 and 2 and Fig. 1).

The non-chemical group, in which rhabdomyolysis was caused by all etiologies other than chemicals, was classified into 3 categories (physical [n = 29], infection [n = 3], and metabolic [n = 7]). Each class was further divided into the following: immobilization (n = 16), overactivity (n = 9), and trauma (n = 4) for the physical class; meningitis (n = 2) and unknown focus (n = 1) for the infection subclass; and hypernatremia (n = 1), hyponatremia (n = 1), hyperthermia (n = 2), and hypoglycemia (n = 3) for the metabolic subclass (Fig. 1).

There were no differences between the patients surviving rhabdomyolysis and those succumbing to the disease with respect to the incidence of ARF or rhabdomyolysis-related laboratory parameters.

DISCUSSION

The principal finding of the current study is that the incidence of rhabdomyolysis was 0.06% (93 of 143,830 admitted patients) in our hospital, which was considerably lower than the incidence (1.8%) in patients with acute pesticide intoxication. Among the 93 cases of rhabdomyolysis, the chemical-induced group accounted for 58% (n = 54) and the non-chemical group for 42% (n = 39). Pesticide intoxication was the leading cause of rhabdomyolysis (35.5%) in these patients.

The incidence and causes of rhabdomyolysis may differ from country to country (18, 19) on the basis of social and environmental factors. The association of rhabdomyolysis with pesticide intoxication was reported in some case reports (11-14), but the current study provides epidemiologic data on this subject. The clinical course of pesticide-mediated rhabdomyolysis was characterized by the early onset. In all of the rhabdomyolysis patients, the diagnosis was confirmed by serum levels of muscle enzymes, which were high enough to suspect rhabdomyolysis in the emergency room. This suggests that the initiation of rhabdomyolysis by pesticide intoxication occurs soon after ingestion.

In our cases of rhabdomyolysis, the levels of myoglobin and muscle enzymes such as CK and lactate dehydrogenase were very high, while the levels of electrolytes such as phosphate, calcium, and potassium were in the normal range. As an initial treatment modality for acute chemical intoxication, we used a

conventional blood purification technique using hemodialysis (AK 95S Hemodialysis Machine [Gambro, Lund, Sweden]; blood flow, 250 mL/min and dialysate flow, 500 mL/min). We believe that the discordance in rhabdomyolysis-related laboratory results for the plasma tests was caused by hemodialysis.

Pesticide-induced rhabdomyolysis may manifest in 3 distinct ways: active toxic compound-induced cellular toxicity, cellular toxicity of additives, and synergistic toxicity from both the active toxic compound and the additives. Our study included 28 patients with acute surfactant intoxication. Among them, 2 patients (7.1%) had rhabdomyolysis (Tables 1 and 2). We have previously described the cell membrane toxicity of surfactants that are frequently included in pesticide formulations (20) and the synergistic toxicity between these surfactants and the actual herbicides (21). On the basis of these findings, we believe that the combined toxicity of surfactants and the chief pesticide ingredient is responsible for the high incidence of rhabdomyolysis in acute pesticide intoxication. Furthermore, the observation that men are more prone to have rhabdomyolysis after pesticide intoxication than women may be related to the differences in sex hormones and muscle mass between men and women.

Some patients died during the progression of rhabdomyolysis. In such situations, we could not determine the extent to which rhabdomyolysis was responsible for the deaths. The deaths may have been the result of synergistic or additive effects of rhabdomyolysis and the pesticide poisoning. Ethanol itself may cause rhabdomyolysis, as is shown in Table 2. In our study, most of the patients who developed rhabdomyolysis in the pesticide class also ingested ethanol. However, there was no difference in the serum alcohol levels measured in the emergency room between the patients with pesticide intoxication who did and did not have rhabdomyolysis. This result suggests that ethanol itself was not responsible for causing rhabdomyolysis in the patients with pesticide intoxication.

The lack of rhabdomyolysis among patients taking statins was notable. During the observation period, 8,486,084 statin tablets were prescribed to 27,902 patients in our hospital. None of these patients developed rhabdomyolysis during their treatment with statins. Although not a focus of the current study, we suspect that pharmacogenetic differences between races may explain this unexpected observation.

Recently, Heyne et al. (22) described high cutoff renal replacement therapy (molecular cutoff at 45 kDa) as a novel approach for the extracorporeal elimination of myoglobin in rhabdomyolysis-associated ARF. However, conservative treatment including hydration with lactated ringer solution, alkalization of urine with bicarbonate, and the addition of mannitol is generally recommended, and nephrotoxic drugs should be avoided.

Our study has some limitations. We could not discern whether rhabdomyolysis or the chemical poisoning was more responsible for ARF because ARF occurred in patients with acute pesticide poisoning and coincident rhabdomyolysis. For similar reasons, we could not determine whether rhabdomyolysis-associated ARF or pesticide poisoning caused death. Despite this limitation, our study determined incidence of rhabdomyolysis in patients with acute pesticide intoxication. In conclusion, pesticide intoxication is a frequent cause of rhabdomyolysis and is more common among men than women. The volume of pesticide ingested, and not the degree of human toxicity, is the main factor influencing the incidence of rhabdomyolysis.

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DISCLOSURE

All of authors have no conflicts of interest to declare.

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