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Original Contribution

The associative factors of delayed-onset rhabdomyolysis in patients with doxylamine overdose

Han Joon Kim MD, PhD[a], Sang Hoon Oh MD[a], Chun Song Youn MD[a], Jung Hee Wee MD[a], Ji Hoon Kim MD[a], Won Jung Jeong MD[a], Soo Hyun Kim MD[a], Seung Hee Jeong MPH[b], Kyu Nam Park MD, PhD[a,*]

[a]*Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul 137-701, Republic of Korea*
[b]*CMC Clinical Research Coordinating Center, Department of Preventive Medicine, The Catholic University of Korea, Seoul 137-701, Republic of Korea*

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Abstract

Objectives: The aim of this study was to investigate the associative factors of rhabdomyolysis in patients with doxylamine overdose who had normal creatine phosphokinase levels at admission.

Methods: This study included 169 patients who visited the emergency department of a tertiary teaching hospital after doxylamine overdose between January 1, 1998, and March 31, 2009. Demographic information, clinical variables, and laboratory data were investigated for the associative factors of rhabdomyolysis.

Results: Thirty-five (21%) of the 169 patients developed rhabdomyolysis. Patients who developed rhabdomyolysis differed from those who did not in the amount of doxylamine ingested, sex, heart rate, initial value of serum creatinine, and alanine aminotransferase. In the multivariate regression analysis, the only reliable predictors of rhabdomyolysis were the amount of doxylamine ingested ($P = .004$) and heart rate ($P < .001$).

Conclusion: Observation and laboratory follow-up are required for patients with large reported ingestions or tachycardia on admission, even if their creatine phosphokinase levels were normal.

1. Introduction

Doxylamine is an over-the-counter drug used primarily as a sleep-inducing agent. Doxylamine has antihistaminic, sedative, and anticholinergic properties [1,2] and is frequently ingested in suicide attempts worldwide, probably because of their ready availability. Doxylamine is relatively safe but is known to cause rhabdomyolysis. Rhabdomyolysis following doxylamine overdose was first reported in 1983 [2]. Some previous studies have reported that incidence of rhabdomyolysis following doxylamine is relatively low [3]. In urban emergency departments (EDs) in Korea, however, doxylamine overdose accounts for 25% of visits due to drug overdose [4]. and the incidence of rhabdomyolysis overdose ranged from 32% to 77% [5-7]. Rhabdomyolysis may result in life-threatening complication due to acute renal failure (ARF) [8-11]. If it is treated promptly, patients can usually recover completely from rhabdomyolysis, and ARF can be prevented. Therefore, the early detection of patients at high

* Corresponding author. Department of Emergency Medicine, Seoul St Mary's Hospital, Seoul, 137-701, Republic of Korea. Tel.: +82 2 2258 1987; fax: +82 2 2258 1997.
E-mail address: emsky@catholic.ac.kr (K.N. Park).

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risk for developing rhabdomyolysis following doxylamine overdose is important. We have noticed that many patients who had normal creatine phosphokinase (CPK) levels at admission developed rhabdomyolysis during observation. However, many patients with doxylamine overdose discharge themselves against medical advice and, in many cases, are discharged without follow-up CPK levels if their CPK levels were normal at admission.

There has been no study conducted on the associative factors for the development of rhabdomyolysis in patients with doxylamine overdose who had normal CPK levels at admission. In this study, we wanted to determine whether patients would require observation based on clinical and laboratory findings at admission.

2. Methods

We retrospectively reviewed the medical records of patients who visited the ED of a tertiary teaching hospital in Seoul, Korea, after an intentional doxylamine overdose between January 1, 1998, and March 31, 2009. Two emergency physicians independently reviewed the medical services records and the psychiatric records. If there were any discrepancies, a third investigator arbitrated these issues. To exclude confounding variables, patients who concurrently ingested other drugs with doxylamine, with the exception of alcohol; experienced a seizure after doxylamine ingestion; and have had history of renal, muscular, central nervous system, ischemic heart disease or significant physical trauma were excluded. Patients who had incomplete data and abnormal CPK levels at admission were excluded.

In all patients, demographic information and clinical variables, including sex, age, medical history, time from drug ingestion to hospital arrival, amount of doxylamine ingested, number of suicide attempts, vomiting, and underlying psychotic disorder were evaluated. Activated charcoal administration and gastric lavage were performed if indicated. Sufficient hydration was conducted for all the patients with doxylamine overdose, and urine alkalization was considered for the cases with CPK level higher than 1000 IU/L. The initial blood samples were sent to the laboratory for blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase (ALT), creatinine, serum electrolyte (sodium, potassium, and chloride), CPK, and lactate dehydrogenase analysis. Urine was collected for pH analysis. Follow-up samples were obtained every 8 to 12 hours. Observation period determined by toxicology manual made independently since 1997. If CPK level increases distinctly, laboratory follow-up was done after observation, even though follow-up laboratory was below 1000 IU/L. Rhabdomyolysis was defined as a serum CPK value greater than 5 times the upper limit of the normal value (>1000 IU/L) [12-14]. This study was approved by the institutional review board of the Catholic University of Korea, Seoul Saint Mary's Hospital.

The results were expressed as mean ± SD or as frequencies (percentages). Comparisons between groups for categorical variables were made using either the χ^2 or Fisher exact test, as appropriate. In addition, continuous variables were compared between groups using the Mann-Whitney U test. Odds ratios and 95% confidence intervals were estimated in the logistic regression model. For the receiver operating characteristic (ROC) curves, the best cutoff value was the optimal point with the highest sum of sensitivity and specificity for predicting the occurrence of rhabdomyolysis. Finally, associative factors were evaluated by multivariate logistic regression analysis. The statistical analyses above were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC). A 2-tailed P value < .05 was considered statistically significant.

3. Results

There were 1544 cases of toxic exposures during the study period, which constituted 0.37% of total ED visits. Of 1544 patients, 283 patients (18.3%) with a doxylamine overdose visited the ED. Sixty-five patients had incomplete data because of self-discharge or discharge without follow-up CPK levels, whereas 49 patients had abnormal CPK levels at admission. These patients were excluded from this study. As a result, a total of 169 patients (male/female ratio, 34:135; mean ± SD age, 31.7 ± 11.9 years) enrolled in this study (Fig. 1). The mean (SD) amount of doxylamine ingested was 19.7 (18.4) mg/kg in body weight, ranging from 0.6 to 173.6 mg/kg. The mean (SD) period of time that elapsed before admission was 182.1 (229.0) minutes, ranging from 15.0 to 1888.0 minutes.

We placed all patients into a rhabdomyolysis group (n = 35) or a nonrhabdomyolysis group (n = 134) and clarified the clinical and laboratory characteristics of rhabdomyolysis patients. In rhabdomyolysis group, rhabdomyolysis (CPK, >1000 IU/L) occurred on 521.0 ± 248.9 minutes (330-1320

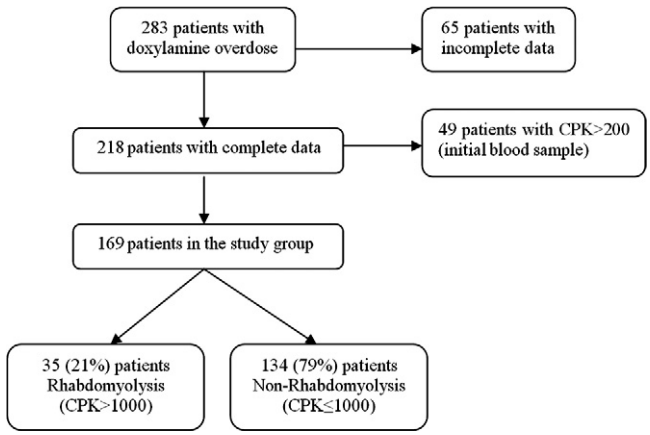

Fig. 1 The number of patients with and without rhabdomyolysis following doxylamine overdose.

minutes) after admission. The longest observation time was 1320 minutes until the CPK levels became higher than 1000 IU/L. Except 3 of the 35 patients, CPK levels became higher than 1000 IU/L within 10 hours in most cases. The maximum value of peak levels of creatinine was 1.18 mg/dL. Acute renal failure did not occur in our study. We think that this result may be due to proper treatment such as sufficient hydration in primary stage and urine alkalization for patients with CPK levels higher than 1000 IU/L.

There were no significant differences in age, alcohol ingestion, vomiting, time elapsed before admission, blood pressure, body temperature, coma, number of suicide attempts, and underlying psychotic disorder between the 2 groups. However, significant differences were found for sex ($P = .001$), amount of doxylamine ingested ($P = .032$), and heart rate ($P < .001$) (Table 1). On admission, laboratory variables of both groups, serum creatinine ($P = .001$), and serum ALT ($P = .005$) were significantly different (Table 2).

Table 1 Clinical variables of patients with and without rhabdomyolysis

Variable	Nonrhabdomyolysis (n = 134)	Rhabdomyolysis (n = 35)	P
Age (y)	32.4 ± 12.9	29.5 ± 7.5	.604
Sex			
Male	20 (14.9)	14 (40.0)	.001
Female	114 (85.1)	21 (60.0)	
Amount of doxylamine ingested (mg/kg)	17.5 ± 13.9	28.5 ± 28.5	.032
Alcohol ingestion	36 (26.9)	9 (25.7)	.891
Prehospital vomiting	12 (9.0)	2 (5.7)	.245
Time elapsed before admission (min)	184.9 ± 236.7	171.9 ± 199.8	.934
Systolic blood pressure (mm Hg)	128.1 ± 20.0	133.5 ± 16.6	.080
Diastolic blood pressure (mm Hg)	78.9 ± 11.7	81.4 ± 11.0	.231
Heart rate (beats/min)	89.7 ± 16.8	103.1 ± 20.0	<.001
Temperature (°C)	36.7 ± 2.4	36.5 ± 0.4	.749
Coma	3 (2.2)	0 (0)	.372
Gastric lavage	103 (76.9)	31 (88.6)	.128
Activated charcoal	122 (91.0)	32 (91.4)	.261
ARF (creatinine, >1.4)	0 (0)	0 (0)	.999

Values are expressed as mean ± SD and n (%).

Table 2 Admission laboratory variables related to the development of rhabdomyolysis

Variable (normal value)	Nonrhabdomyolysis (n = 134)	Rhabdomyolysis (n = 35)	P
CPK (26-200 U/L)	97.8 ± 35.9	114.7 ± 43.1	.053
LDH (250-450 U/L)	366.8 ± 81.3	359.2 ± 65.0	.904
BUN (7-20 mg/dL)	10.5 ± 4.1	10.8 ± 3.6	.491
Creatinine (0.6-1.2 mg/dL)	0.8 ± 0.2	0.9 ± 0.2	.001
AST (14-40 U/L)	20.0 ± 11.5	20.0 ± 8.5	.816
ALT (9-45 U/L)	17.9 ± 10.5	24.8 ± 18.2	.005
Urinary pH (4.8-7.5)	6.2 ± 0.9	5.9 ± 0.8	.060

LDH indicates lactate dehydrogenase; BUN, blood urea nitrogen; AST, aspartate aminotransferase.

To investigate the associative factors of rhabdomyolysis in patients with doxylamine overdose who had normal CPK levels at admission, potential associative factors including sex, the amount of doxylamine ingested, heart rate, initial value of ALT, and creatinine were examined using the multivariate logistic regression analysis (Table 3). The amount of doxylamine ingested ($P = .004$) and heart rate ($P < .001$) were significant associative factors of rhabdomyolysis. Development of rhabdomyolysis was associated with the amount of doxylamine ingested (≥13 mg/kg), with a sensitivity of 85.7%, a specificity of 42.5%, a positive predictive value of 28.0 %, and a negative predictive value of 91.9 %. Fig. 2 shows the ROC curve for various doxylamine doses ingested in the development of rhabdomyolysis following overdose. The area under the ROC curve was 0.703. Rhabdomyolysis in patients was associated with heart rate (≥100 minutes), with a sensitivity of 60%, a specificity of 79.1%, a positive predictive value of 42.9 %, and a negative predictive value of 88.3 %. Fig. 3 shows the ROC curve for various heart rates in the development of rhabdomyolysis following overdose. The area under the ROC curve was 0.702.

Table 3 Associative factors correlated with the development of rhabdomyolysis in patients with doxylamine overdose who had normal CPK levels at admission

Variable	Odds ratio	95% CI	P
Heart rate (≥100/min)	4.885	2.014-11.849	<.001
Amount of doxylamine ingested (≥13 mg/kg)	5.476	1.716-17.475	.004

CI indicates confidence interval

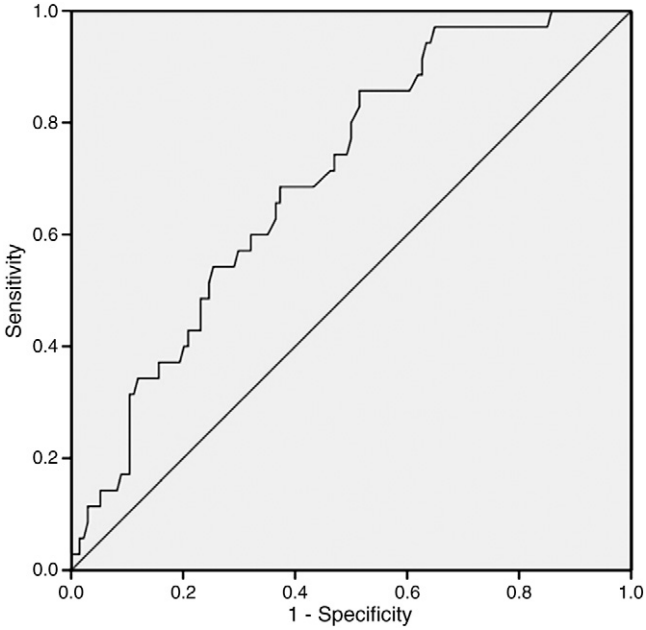

Fig. 2 Receiver operating characteristic curve of the amount of doxylamine ingested in predicting the development of rhabdomyolysis. The area under the ROC curve was 0.703.

4. Discussion

This is the first study of the associative factors for the development of rhabdomyolysis in patients with doxylamine overdose with normal CPK levels at admission. Doxylamine is an ethanolamine derivative and has a peak plasma concentration of 0.1 mg/mL in 2 to 3 hour after an oral administration of a standard dose of 25 mg. Most of the drug (60%) excreted unchanged in the urine, and the remainder is metabolized through various metabolic pathways with a half-life of approximately 10 hours [15]. The diagnosis of sedating antihistamine poisoning is based on a positive history of ingestion and physical findings consistent with the anticholinergic syndrome. The most common manifestations of antihistamine overdose are related to their anticholinergic effects. These include variable levels of central nervous system depression, hallucination, convulsion, tachycardia, arrhythmia, mydriasis, hyperthermia, skin flushing, and hypotension [16]. Absence of tachycardia shortly after anticholinergic poisoning suggests an inaccurate history or coingestion of a cardiotoxic agent [17].

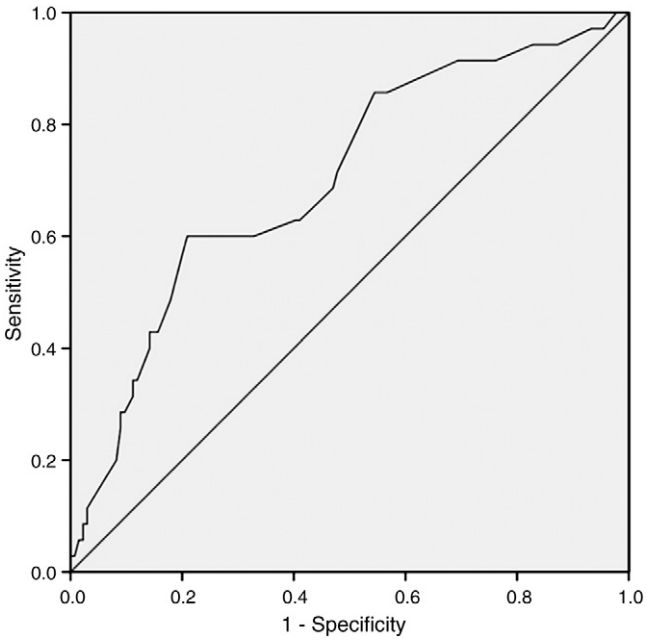

Fig. 3 Receiver operating characteristic curve of heart rate in predicting the development of rhabdomyolysis. The area under the ROC curve was 0.702.

Aside from anticholinergic effects, rhabdomyolysis following doxylamine overdose was reported in the literature [2-6]. Therefore, observation is necessary to see whether or not rhabdomyolysis develops in symptomless patients. However, the emergency department is often crowded, so observation for all patients who ingested relatively small amounts of doxylamine and had CPK levels within the reference range at admission is not possible practically. Furthermore, most of these patients usually discharge themselves against medical advice and, in many cases, are discharged without follow-up CPK levels if their CPK levels were normal at admission. In this study, many patients discharged themselves, and we also found that rhabdomyolysis even developed in 21.0% (35/169) of patients who had CPK levels within the reference range at admission. Therefore, it is important to know the severity of the adverse effects and to decide which patients with normal CPK levels at admission require more observation.

An elevated serum CPK level is the most sensitive and reliable indicator of muscle injury. The degree of CPK elevation correlates with the amount of muscle injury and severity of illness. Most investigators consider a 5-fold or greater increase in serum CPK, without cardiac or brain injury, as the requirement for making the diagnosis of rhabdomyolysis [12-14]. Therefore, we defined rhabdomyolysis as a serum CPK value greater than 5 times the upper limit of the normal value (>1000 IU/L).

The amount of doxylamine ingested, sex, heart rate, initial creatinine level, and initial ALT level showed a significant association with rhabdomyolysis in the univariate analysis. Although the mechanism for rhabdomyolysis in doxylamine overdose is uncertain, drug-induced rhabdomyolysis generally can be explained by 2 mechanisms, direct drug injury to the striated muscle and local muscle compression in coma, seizures, and metabolic abnormalities [18-20]. We believe that higher amounts of doxylamine ingestion in male (male vs female: 20.7 ± 29.9 mg/kg vs 19.5 ± 14.3 mg/kg, P = .745) and differences in muscle mass between sexes may be the causes of this result. Alcohol ingestion, which is one of the assumed factors, was not a significant factor in this study [21,22]. Jo et al [7]

suggested that a relatively small amount of alcohol ingested does not increase the risk of rhabdomyolysis following doxylamine overdose. This reason, as well as inaccuracies in patient self-reporting without estimation of serum concentration, may be the cause of this discrepancy in our study.

In the multivariate regression analysis, the amount of doxylamine ingested and initial heart rate were reliable associative factors for the development of rhabdomyolysis. This correlated with findings from recent report that the amount of doxylamine ingested was a reliable predictor for the development of rhabdomyolysis. Jo et al [7] concluded that ingestion of more than 20 mg/kg is the only reliable predictor for developing rhabdomyolysis, but our cutoff value was lower than that of the other study because we excluded patients who had already developed rhabdomyolysis upon arrival at the ED. We believe that our observation cutoff value is better suited for application in the ED than the other value. Sinus tachycardia is one of the earliest and most reliable signs of muscarinic receptor blockade of doxylamine [20]. Therefore, we suggest that sinus tachycardia is an associative factor for developing rhabdomyolysis, too. Our study suggests that observation and laboratory follow-up are required for patients with large reported ingestions or tachycardia on admission, even if their CPK levels at admission were normal. In addition, the possibility of rhabdomyolysis is likely to be higher in male with creatinine level higher than 1 mg/dL, urine pH below 6.0, or ALT level higher than 20 U/L according to their initial laboratory values.

We recognize several limitations in the interpretation of our findings. First, some of the data that were collected with self-reporting were likely not accurate. Second, although it may have been that those who presented with a reduced conscious state had a higher likelihood of developing rhabdomyolysis due to immobility and muscle compression, we could not check the conscious state of all patients accurately. Third, data were incomplete for 25% of cases with reported doxylamine exposure. This should be acknowledged as a potential weakness of the study.

5. Conclusion

This retrospective chart review suggests that clinicians caring for patients with large reported ingestions or tachycardia on admission should have a high degree of vigilance for the development of delayed rhabdomyolysis. Observation and laboratory follow-up are required for these patients, even if their CPK levels were normal.

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