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원 저

급성 글루포시네이트 암모늄 중독환자에서 혈중 Neuron specific enolase 수치와 경련발생 간의 연관성

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Relationship between Serum Neuron Specific Enolase Level and Seizure in Patients with Acute Glufosinate Ammonium Poisoning

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Purpose: Glufosinate ammonium poisoning can cause seizures, even after a symptom-free period. This study was conducted to evaluate the relationship between serum neuron specific enolase (NSE) level and the occurrence of seizures in patients with acute glufosinate ammonium poisoning.

Methods: For this retrospective observational study, data from patients diagnosed with acute glufosinate ammonium poisoning were collected between January 2016 and June 2016. Serum NSE was measured within 2 hours of arrival at the emergency department. The patients were divided into a seizure group and a non-seizure group.

Results: The seizure group included eight of the 15 total patients (53.3%). The serum NSE level was significantly higher in the seizure group than in the non-seizure group (32.4±11.9 ng/mL vs. 19.5±5 ng/mL, p=0.019). The amount of glufosinate ingested and initial and peak serum ammonia levels were significantly higher in the seizure group than in the non-seizure group. There was no significant difference in the area under the curve of the serum NSE level or the initial and peak serum ammonia levels in terms of predicting the occurrence of seizures.

Conclusion: In acute glufosinate poisoning, initial serum NSE levels may help in prediction of seizures.

Key Words: Biomarkers, Complications, Herbicides

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Introduction

Glufosinate is a glutamate analog that inhibits glutamine synthetase in plants, which blocks the synthesis of glutamine from glutamate and ammonia[1]. Herbicides containing glufosinate ammonium are available in many countries and their use has gradually increased[2]. Acute glufosinate ammonium poisoning can cause seizure in humans[2]. Sudden developed seizure can rapidly deteriorate the patient's condition during hospitalization. Therefore, acute glufosinate ammonium-poisoned patients should be carefully observed for several days after ingestion.

In acute glufosinate ammonium poisoning, the use of a biomarker for predicting seizure can be helpful to indicate the prognosis of patients, because seizures can occur after latent periods following ingestion[2-4]. Neuron specific enolase (NSE) has been widely evaluated as a predictive marker of neuronal cell damage after traumatic and hypoxic brain damage, status epilepticus, carbon monoxide poisoning, and cardiac arrest, because NSE is not physiologically secreted unless damage to brain cells occurs[5-11]. NSE is a glycolytic enzyme that is predominantly localized in the neuronal cytoplasm in the central nervous system. There are three isozymes of enolase: enolase α is ubiquitous, enolase β is muscle-specific, and enolase γ is neuron-specific[12,13]. Whereas the $\gamma\gamma$ form of NSE is expressed in neurons, the $\alpha\gamma$ form is expressed in the glial cells, such as microglia, oligodendrocytes, and astrocytes[14,15]. Therefore, the $\alpha\gamma$ and $\gamma\gamma$ forms of NSE can be released from the neuronal and glial tissues into blood when cell membrane integrity is lost. However, studies regarding the relationship between serum NSE and seizures are limited in acute glufosinate ammonium poisoning.

Therefore, the aim of this study was to evaluate the relationship between serum NSE level and the occurrence of seizures in patients with acute glufosinate ammonium poisoning.

Methods

1. Study design and patients

For this retrospective observational study, data of consecutive adult patients (〉18 years) diagnosed with acute glufosinate ammonium poisoning was collected between January 2016 and June 2016. The emergency department (ED) was located in a single, suburban, tertiary-care hospital with more than 46,000 annual visits, and is staffed 24 hours a day by board-certified emergency physicians.

Acute glufosinate ammonium poisoning was confirmed by patient or guardian statements and an emergency physician verified the agent and transcribed the bottle label into the patient record. All acute glufosinate ammonium-poisoned patients were admitted to the intensive care unit for close observation for more than one day. Patients with hyperammonemia received a lactulose enema to lower the ammonia level because high levels may cause neurological complications[4].

Patients were excluded from the study for the following reasons: 1) poisoning with any additional material except for alcohol; 2) the presence of other conditions that could increase serum NSE, including hemolyzed blood, neural chest-derived tumors like small cell lung cancer, neuroendocrine tumor, and cardiac arrest before arriving at the ED[16,17]; 3) no serum NSE levels were taken; 4) presentation more than 24 hours after acute poisoning because the half-life of serum NSE is 24 hours[9]; and 5) transfer to another hospital after admission into the ED.

This study was approved by the Institutional Review Board at Wonju Severance Christian Hospital (approved number: CR317360).

2. Study variables and definitions

The following clinical variables were evaluated: age; sex; intentionality of poisoning; ingested amounts (cc); time elapsed from ingestion to ED arrival (hours); co-ingestion of alcohol; medical history; initial vital signs; initial symptoms; and complications, such as seizures, mental changes (Glasgow Coma Scale, GCS〈13), amnesia, respiratory failure, pneumonia, and shock. Intensive care unit (ICU) admission days and in-hospital mortality were also evaluated. Respiratory failure was defined as hypoxia (PaO_2〈70 mmHg) or hypercapnea ($PaCO_2$〉60 mmHg). Shock was defined as systolic blood pressure less than 90 mmHg requiring administration of a vasoactive drug.

Laboratory variables included serum NSE, serum ammonia level, arterial blood gas analysis, and serum lactate. Serum NSE levels (reference range: 〈16.3 ng/mL) were obtained using Cobas® (Roche Diagnosis, Indianapolis, IN, USA) and were measured within 2 hours after arrival at the ED. We checked serum ammonia level (reference range: 〈54

μg/dL) because the measurement of serum ammonia level has been suggested as an indicator of neurologic complications including seizure in glufosinate ammonium poisoning[4,18,19]. Serum ammonia levels were serially measured once more within 24 hours after arrival at the ED and were followed until normalization. The peak ammonia level was defined as the highest serum ammonia level measured. The patients were divided into two groups: the seizure group and the non-seizure group.

Data were collected during a retrospective review of patient electronic medical records by one emergency physician who was blinded to the study objectives and hypothesis. The abstractors were blinded to the categorization of the patient groups. Because the study was performed retrospectively and observationally, the patient records and information were anonymously processed prior to analysis.

3. Study endpoint

The primary outcome of this study was to compare serum NSE levels associated with the occurrence of seizures in acute glufosinate ammonium poisoning.

4. Statistical analysis

Data are expressed according to the properties of the variable. Continuous variables are presented as the mean and standard deviation or the median and range. Categorical variables are shown as a frequency and percentage. A Chi-square test (Fisher' s exact test) was used to compare the categorical variables and two sample t- or Mann-Whitney U-tests were used to compare the continuous variables. Normality was first assessed using the Shapiro-Wilk test. The area under the receiver operating characteristic (ROC) curve was used to evaluate the ability of serum NSE to determine the occurrence of seizures. In addition, comparison of the area under the curve (AUC) was analyzed using the method of DeLong et al. A *p*-value less than 0.05 was considered statistically significant and all statistical analyses were conducted using SPSS ver. 23 (IBM, Armonk, NY, USA) and the MedCalc Statistical Software version 17.5.3 (MedCalc Software, Ostend, Belgium).

Results

1. Patient characteristics

During the study period, 15 consecutive patients with acute glufosinate ammonium poisoning were identified and all patients were included. In all patients, the ingested glufosinate concentration was 18% and sodium laureth sulfate and sodium lauryl sulfate were contained as surfactants.

Eight patients (53.3%) were men and the mean age was 58.4 years. The poisoning was intentional for all patients, and the patients arrived at the ED within a median of 3 hours after ingestion. Diabetes mellitus (20%) and hypertension (26.7%) were common past medical conditions. Patients experienced nausea/vomiting (60%), dizziness (40%), and dyspnea (20%) at the ED. All patients received gastric irrigation or gastric lavage and activated charcoal. Mental changes (12 patients, 80%), amnesia (9 patients, 60%), and seizures (8 patients, 53.3%) were common during hospitalization. One patient died during hospitalization (Table 1).

2. Comparisons between non-seizure group and seizure group

The seizure group included 8 patients (53.3%). On the hospital admission day 0, 4 patients experienced seizures and the rest occurred on the hospital admission day 1. The amount ingested, serum NSE level, and initial and peak serum ammonia levels differed between the groups (Table 1 and Figure 1). Although the AUC of initial serum ammonia to predict the occurrence of seizures was higher than AUC of the serum NSE or peak serum ammonia levels, there was no significant difference among each tests (Table 2 and Figure 2).

All complications, including mental change, respiratory failure, pneumonia, shock, and in-hospital mortality, more developed in the seizure group, although

there was no significant difference, except for amnesia. The ICU admission duration was significantly longer in the seizure group than in the non-seizure group (Table 1).

Discussion

Glufosinate ammonium herbicide can cause seizure as neurologic complication through excitation and depression of the central nervous system by glufosi-

Table 1. Baseline characteristics and laboratory findings in patients with acute glufosinate ammonium poisoning

	Total (n=15)	Non-seizure group (n=7, 46.7%)	Seizure group (n=8, 53.3%)	*p*-value
Age	58.4±15.3	58.6±14.6	58.3±17	0.969
Male	8 (53.3)	3 (42.9)	5 (62.5)	0.619
Ingested amounts (cc)	235±140	147±89	313±133	0.015
ED visit time (hours)	3 (2-4.5)	3 (1-4)	2.5 (2-5)	0.613
Co-ingested alcohol	7 (46.7)	4 (57.1%)	3 (37.5)	0.619
Medical history				
DM	3 (20)	1 (14.3)	2 (25)	1.000
HTN	4 (26.7)	2 (28.6)	2 (25)	1.000
Hyperlipidemia	1 (8.3)	0 (0)	1 (12.5)	1.000
Vital signs				
SBP (mmHg)	119 (110-156)	142 (109-158)	119 (110-152)	0.613
PR (rates/minute)	97 (91-108)	92 (78-110)	104 (92-161)	0.281
RR (rates/minute)	18 (18-19)	18 (18-20)	18 (16-19)	0.281
BT (˚C)	36.2 (35.9-36.8)	36.2 (36-36.8)	36.2 (34.9-37.5)	0.867
Symptoms and signs				
Nausea/vomiting	9 (60)	3 (42.9)	6 (75)	0.315
Abdominal pain	3 (20)	0 (0)	3 (37.5)	0.200
Headache	2 (13.3)	0 (0)	2 (25)	0.467
Dizziness	6 (40)	3 (42.9)	3 (37.5)	1.000
Dyspnea	3 (20)	2 (28.6)	1 (12.5)	0.569
Laboratory findings at the ED				
ABG				
pH	7.39 (7.31-7.4)	7.35 (7.33-7.4)	7.39 (7.12-7.42)	0.867
PaO_2 (mmHg)	105 (103-129)	111 (105-135)	103 (91-162)	0.281
$PaCO_2$ (mmHg)	32.4 (30.1-34.4)	30.4 (28-38.1)	32.9 (31.5-34.9)	0.536
Bicarbonate (mmol/L)	20.1 (16.5-20.7)	20.1 (17.6-20.8)	19.9 (11.6-20.9)	0.867
Lactate (mmol/L)	2.73 (1.96-3.27)	2.73 (1.36-2.84)	2.96 (1.41-6.34)	0.867
NSE (ng/mL)	26.3±11.2	19.5±5	32.4±11.9	0.019
Initial ammonia (㎍/dL)	119±57	69±21	162±41	<0.001
Peak ammonia (㎍/dL)	132±55	95±47	165±38	0.007
Complications				
Mental change	12 (80)	4 (57.1)	8 (100)	0.077
Amnesia	9 (60)	2 (28.6)	7 (87.5)	0.041
Respiratory failure	5 (33.3)	2 (28.6)	3 (37.5)	1.000
Pneumonia	6 (40)	1 (14.3)	5 (62.5)	0.119
Shock	3 (20)	1 (14.3)	2 (25)	1.000
ICU admission days	7.5±5.5	2.9±1.1	11.7±4.2	<0.001
In-hospital mortality	1 (6.7)	0 (0)	1 (12.5)	1.000

ED: emergency department, DM: diabetes mellitus, HTN: hypertension, SBP: systolic blood pressure, PR: pulse rate, RR: respiratory rate, BT: body temperature, ABG: arterial blood gas, PaO_2: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide, NSE: neuron specific enolase, ICU: intensive care unit

mean±standard deviation

median (interquartile range)

Table 2. Values of receiver operating characteristic curves for serum NSE and ammonia levels for predicting seizures in patients with acute glufosinate ammonium poisoning

Variables	AUC (95% CI)	*p*-value (vs. NSE)	*p*-value (vs. Initial ammonia)	*p*-value (vs. Peak ammonia)
NSE	0.857 (0.584-0.980)	-	0.256	0.818
Initial ammonia	0.982 (0.752-1.000)	0.256	-	0.265
Peak ammonia	0.893 (0.628-0.991)	0.818	0.265	-

AUC: area under the curve, CI: confidence interval, NSE: neuron-specific enolase

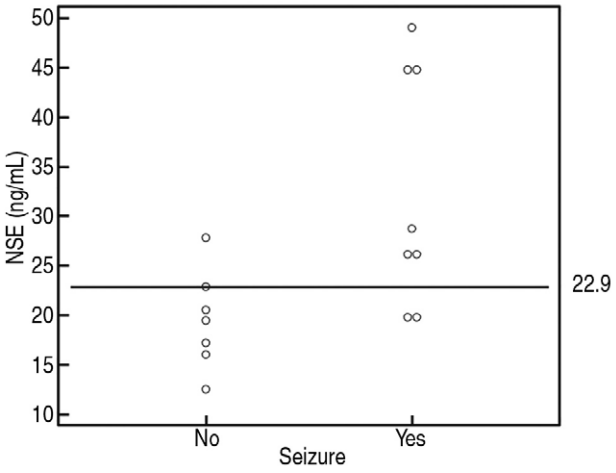

Fig. 1. Serum NSE levels at the emergency department in patients with acute glufosinate ammonium poisoning classified according to presence of seizure.
22.9 ng/mL means cut-off value of serum NSE according to presence of seizure
NSE: neuron-specific enolase

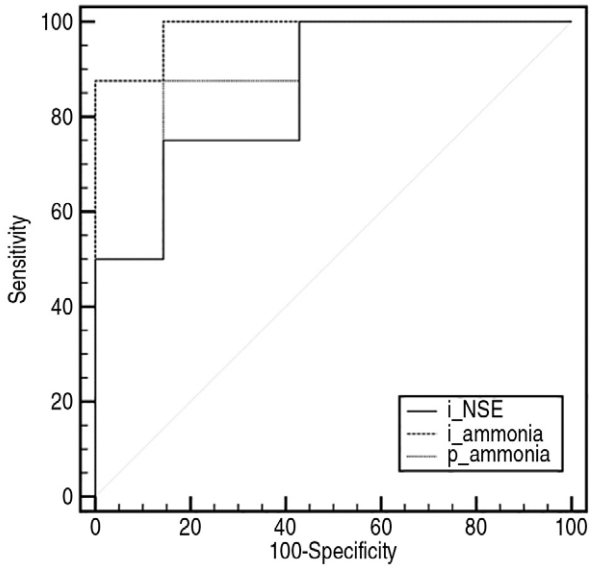

Fig. 2. Receiver operating characteristic curve of the serum NSE level to predict neurologic features.
NSE: neuron-specific enolase

nate, its metabolites, surfactants, or glufosinate-induced imbalance between glutamate, ammonia, and glutamine[18,20]. The toxic mechanism is mediated through the N-methyl-D-aspartate receptor, which increases intracellular calcium ions and nitric oxide[21]. This effect can inhibit glutamine synthetase in the nearby astrocytes, which are the most abundant cell type within the brain, and result in accumulation of glutamate and ammonia[22]. The associated intracellular accumulation of ammonia causes tissue necrosis and death in the brain[4,19]. In this study, the seizure was developed in 53.3% and serum NSE, which may be released from the neuronal and glial tissues into the blood when cell membrane integrity is lost, was significantly higher in the seizure group. A seizure is a sudden change in behavior caused by abnormal excessive or synchronous neuronal activity in the cerebral cortex. Within the brain, oxygen consumption is highly dynamic and region specific. The cerebral cortex consists of an outer zone of neural tissue called the gray matter and gray matter consumes more than twice as much oxygen as the white matter, with the highest consumption occurring in the medial occipital lobe[23]. Because so much oxygen is consumed in the cerebral cortex, the cerebral cortex may be also vulnerable to other toxic insults. Therefore, NSE may be released in a greater amount in the brain cells of the cerebral cortex and reflect injury to the cerebral cortex related to seizures. However, we could not know whether serum NSE concentration would predict seizures in acute glufosinate ammonium poisoning due to small sample, although a few studies have indicated the usefulness of serum NSE in predicting human epilepsy[6,24]. Therefore, a well-designed prospective study is necessary to address

this limitation.

In previous reports, the serum ammonia level was also a good predictor of neurologic complications, including seizures[3,4]. In present study, serum ammonia was also significantly higher in the seizure group than in the non-seizure group. If the arterial ammonia level is elevated, an increased uptake of ammonia by the brain cells can occur[25], and this reaction can be promoted by the formulation of anionic surfactants contained in glufosinate herbicide as anionic surfactants can increase the uptake of ammonia into the brain by increasing the permeability of the blood-brain barrier[26].

In this study, the ingested amount was statistically higher in the seizure group than in the non-seizure group. In our previous study and a study by Moon et al., the ingested amount was significantly higher in the neurological complication group including seizure than in the non-neurological complication group[4,27]. However, in studies by Mao et al. and Inoue et al., the ingested amounts were not statistically different between the non-neurological complication group and the neurological complication group[19,28]. This difference may have occurred because it is difficult to accurately measure the amount ingested. In this study, all other complications, including mental changes, amnesia, respiratory failure, pneumonia, shock, and in-hospital mortality, occurred more frequently in the seizure group. In addition, patients who experienced seizures were more often admitted to the ICU than patients who did not experience seizures. Therefore, if other complications occur, the patients should be treated more intensively.

This study had several limitations. First, the number of patients was small because the study was limited to a single-center. However, we evaluated all patients with acute glufosinate ammonium poisoning and measurement of serum NSE to reduce this possible bias. Serum NSE was checked from January 2016 to June 2016 in the ED. Second, the study was limited by its retrospective design. Missing data during collection was also a limitation. Third, we could not exclude the effects of the contained surfactant. However, in all patients, the ingested surfactants were sodium laureth sulfate and sodium lauryl sulfate. Fourth, we did not measure serial NSE levels like we did serum ammonia levels. Therefore, we could not evaluate the serial changes in the serum NSE levels poisoned patients. Fifth, a patient's initial mental status can be affected by the co-ingestion of alcohol, and respiratory failure and shock affecting cerebral perfusion and oxygenation. However, there was no significant difference in the incidence of alcohol co-ingestion, and respiratory failure and shock between the non-seizure group and the seizure group. Sixth, hemolysis may cause an increase in the serum NSE level proportional to the degree of hemolysis, even in the absence of brain injury[29]. However, laboratory markers of hemolysis, including serum total bilirubin and lactate dehydrogenase levels were not significantly different between the non-seizure group and the seizure group. Seventh, we could not diagnose the non-convulsive seizures and completely differentiate seizures from myoclonus because we did not confirm the seizure through electroencephalography.

Conclusion

In acute glufosinate poisoning, initial serum NSE levels may be helpful for predicting seizures.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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