

# A case of status epilepticus developed after Alpha Lipoic Acid intake

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## Abstract

**Introduction:** Alpha Lipoic Acid (ALA) is an antioxidant used in diabetic neuropathy. It is not prescribed to children. However, rarely, intoxication may occur due to accidental or suicidal intake. **Case report:** A 16-month-old child presented with confusion after taking 1800 mg of ALA. Convulsions that did not respond to midazolam and levetiracetam started in the emergency room. He was admitted to the intensive care unit and was intubated. Convulsions could be controlled with intravenous Ketamine infusion. He received mechanical ventilation support for five days. Gastrointestinal bleeding developed during follow-up and was treated with pantoprazole. There were laboratory measurements consistent with metabolic acidosis. Central nervous system imaging and cerebrospinal fluid examinations were normal. Electroencephalograms taken under elective conditions were reported as normal for his age. He was discharged on the twelfth day of his hospitalization. **Conclusion:** Children and adults with suspected ALA intake should be referred to tertiary healthcare facilities as soon as possible. In the first stage, gastric lavage and activated charcoal should be applied. Since there is no specific antidote, it should be prepared to deal with resistant convulsions, metabolic acidosis, and multi-organ failure in addition to general supportive therapy.

**Keywords:** Alpha-Lipoic Acid, INFANT, Poisoning, Status Epilepticus, Ketamine.

## INTRODUCTION

Alpha Lipoic acid (ALA) is an antioxidant-effective drug [1]. Reactive oxygen and nitrogen oxide species are produced as byproducts of oxidative metabolism. Its main functions have been reported as an immunological host defense. However, it has potential damage to high levels of cellular macromolecules. ALA has the ability to directly reduce free radicals [2]. It is mainly used in diabetic neuropathy patients because of this feature [3]. Also, there are studies suggesting that it should be used for breast cancer, after spinal cord injury and to reduce the side effects of chemotherapy drugs [4]. We have been able to reach seven cases reported so far regarding the rare ALA intoxication [5-11]. We report a rare case with ALA intoxication.

## CASE REPORT

A 16-month-old male patient was presented to our emergency

department with a complaint of taking 3 ALA tablets of 600 mg, 3 hours ago. It was learned that from the referral form, he was presented to the emergency department of the external center with confusion in the first hour, 1 mg/kg activated charcoal was administered there, 5 mg rectal diazepam was given for his tonic-clonic convulsion lasting 15-20 seconds and referred to us for further follow-up. He was no history of trauma or convulsion, and his mother had epilepsy. When the patient was admitted, O<sub>2</sub> saturation was measured at 100%, heart rate 160/min, body temperature 36.7 C and arterial blood pressure 110/70 mmHg.

Athetoid involuntary movements began in four extremities at the first hour of admission. Meanwhile, no saturation change was observed. After continuing for more than a minute, 0.1 mg/kg midazolam was administered intravenously. Due to his involuntary movements did not stop, midazolam infusion was started at 0.07 mg/kg/hour and the child was admitted to the intensive care unit. Since his convulsions did not stop, the midazolam infusion rate was increased to 0.1 mg/kg/hour, but it

continued.

Blood pH 7.19, pCO<sub>2</sub> 32.4 mmHg, and HCO<sub>3</sub> 12.2 mmol/L were measured, consistent with metabolic acidosis. The INR test result was 1.57, so five mg Vitamin K was administered intravenously. Other laboratory values include blood glucose

209 g/dL, LDH 344 U/L (n 135-214), Phosphorus 2.66 mg/dL (n 3.2-5.7), Troponin 39.8 (n 0-14). WBC 22.59 K/uL, NEU% 77.6, HGB 12.4 gr/dL, MCV 57.0, D-Dimer 275 (n 0-243), Fibrinogen 181 mg/dL (n 200-393), PTZ (Second) 18.5 (n 10.2-14.4), PTZ (INR) 1.57 was measured abnormally compared to the reference values. Other tests were normal (Table 1).

**Table 1:** Laboratory values of the case by days.

Laboratory Data	1 Day	2 Day	3 Day	4 Day	5 Day	6 Day	7 Day	8 Day	9 Day	Normal Values
Glucose	209	56-92	145-86	111-127	127	98	99	88	96	60- 100 mg/dL
pH	7.194	7.376-7.34	7.452-7.255	7.426-7.45	7.34	7.468	7.385	7.387	7.40	7.350 7.450
HCO <sub>3</sub> (std)	12.6	14.4-19.7	21-18.5	23.1	22.3	23.9	22	23.1	24.9	21-29 mmol/L
CO <sub>2</sub>	32.4	17.1-45	35.1	28.2	43.8	34.8	37.3	40.4	41.6	35- 45 mmHg
Lactate	7.7	1.62	1.29	-	-	1.34	1.22	1.32		0.7- 2.1 mmol/L
WBC	22.59	15.41	20.14	14.89	17	10.66	13.37	12.09	9.95	4- 10 K/uL
HGB	12.4	12	11.8	7	10.6-13.9	12.9	12.4	11.9		11- 16 gr/dL
PLT	458	339	300	204-142	187	199	284	-	572	150- 300 x1000/mm <sup>3</sup>
INR	1.57	1.51	1.46	1.38	1.14	-	-	-	-	0.85- 1.2
Troponin	39.8	8.64	10.4	-	-	-	-	-	-	0- 14 ng/mL
D-DIMER	273	268	193	-	-	-	-	-	-	0-243 ng/mL DDU
AST	33	49	46	90	107	115	59	45	33	IU/L <32
ALT	16	23	28	60	72	95	70	59	44	IU/L <33
Vitamin B12		743								>200 ng/L
Urine ketone	++	+	+							
Urine Glucose	++++									
Urine protein			+							
Urine hemoglobin			+++							
CSF Glucose			68							mg/dL (45-80 mg/Dl)
CSF Protein			16							g/L (n:20-40mg/dL)
CSF culture					negative					
CSF PCR				negative						
Blood culture							negative			
Urine culture			negative							

Abnormal values are marked in bold. CSF: Cerebro Spinal Fluid

National Poison Information Center (number 114) was consulted. It was reported that there was no specific treatment or antidote. Cardiac monitoring, symptomatic treatment, and asymptomatic 24-hour follow-up was recommended. Since the patient continued to have convulsions while receiving the midazolam infusion, an IV loading of levetiracetam 20 mg/kg was performed, and maintenance was initiated at 20 mg/kg/day. Because of his convulsions, tachycardia, and bad clinical condition progressed, the patient was accepted as status epilepticus and was intubated. Although midazolam was increased to 2 mg/kg/hour, his convulsion did not stop. Then, ketamine was started at a dose of 10 mcg/kg/minute and the convulsion was controlled. Contrast-enhanced and diffusion cranial MRI was performed to exclude encephalitis and increased intracranial pressure. No pathology was found in the MRI. The urine toxicology test was negative.

On the second day, the patient was followed up on mechanical ventilation. His metabolic acidosis continued with blood pH 7.33, pCO<sub>2</sub> 20 mmHg, and HCO<sub>3</sub> 10 mmol/L. Fluid therapy was set at 2000 cc/m<sup>2</sup>/day and NaHCO<sub>3</sub> administration was continued until the blood HCO<sub>3</sub> level recovered. Nifedipine treatment was given because the arterial blood pressure was above the 99 percentiles. In follow-up examinations, blood leukocyte, glucose, electrolyte, and troponin values improved.

On the third day, the patient was followed up on mechanical ventilation. C Reactive protein increased above normal values with 8.08 mg/L (n <5). The INR value decreased compared to the previous day. Lumbar puncture was performed due to the patient's persistent fever that rose to 38 degrees. Cerebrospinal fluid (CSF) biochemistry was normal. No cells were seen in the direct and stained examination. No grow was detected in the

urine culture. It was planned to discontinue the patient's midazolam dose by reducing it. In the complete urinalysis, glucose was lost, ketone + persistence, and + leukocyturia, +++ hemoglobinuria, and + proteinuria started.

He was followed up on mechanical ventilation on the fourth day. Hemoglobin was measured as 7 g/dL, then 15 cc/kg erythrocyte replacement therapy was given. Midazolam was discontinued on the fifth day. Ketamine treatment was halved at 5 mcg/kg/min. CSF culture was reported as negative. Hemoglobin was measured as 10.7 g/L, but because of active lower gastrointestinal (GIS) bleeding, erythrocyte replacement was performed again. Omeprazole 2 mg/kg/day IV 24-hour infusion was initiated. In biochemistry tests, AST increased by 90 U/L, and ALT increased by 60 U/L. Occult blood was positive, and rare erythrocytes and leukocytes were found in the stool. He has been melaena three times. The patient's response to the painful stimulus in the form of spontaneous eye opening and crying was observed for a short time. Mechanical ventilation was stopped and extubated.

On the sixth day of his hospitalization, he started responding to verbal stimuli. Enteral feeding was initiated after GIS bleeding stopped. The omeprazole dose was cut in half. He was transferred to the general children's service. On the twelfth day of his first admission, he was discharged with a prescription of omeprazole 1x10 mg/day and levetiracetam 20 mg/kg/day.

On the twentieth day after the first admission and in the third month, 18-channel bipolar, longitudinal, transverse, and reference montage, digital EEG recordings reported the as compatible with the age and normal, and antiepileptics were discontinued.

## DISCUSSION

Intoxication of 4 children [7, 8, 10, 11] and 3 adults [5, 6, 9] has been reported in the literature up to date. Our case was in a status epilepticus similar to the previous pediatric cases, his seizure did not respond to classical anticonvulsants and, unlike the previous cases, he stopped with ketamine infusion.

It has been reported that ALAs which were accidentally taken by pediatric patients, belongs to an adult diabetic patient at home [8, 10, 11]. One adolescent and 3 adult patients were exposed to suicide purposes and one patient was exposed to toxication because of prescribing error [5-7, 9].

One case reported as fatal. She was suspected of taking norfenefrine and paracetamol in addition to ALA. However, since the paracetamol level is low and the toxicity of norfenefrine has not been reported, multi-organ failure has been attributed to ALA [7]. All other cases were discharged without any sequelae.

There are no human studies on the toxic dose of ALA. In a study conducted in the rhesus monkey liver, the LD<sub>50</sub> dose was reported as 90-100mg/kg [12]. In another study conducted by Fuke *et al.* with rats, they determined the LD<sub>50</sub> dose as 1320 mg/kg in male rats and 1130 mg/kg in female rats [13]. Cremer *et*

*al.* reported the LD<sub>50</sub> dose > 2000 mg/kg in their study with Wistar rats [14]. In our case (body weight 10.8 kg), the dose taken was 166.66 mg/kg. In the case reported by Karaarslan *et al.* of similar age, the amount of ALA taken was calculated as 226 mg/kg.

The main clinical findings in the cases, a spectrum that starts with loss of consciousness, lethargy, involuntary movements, convulsions, central nervous system findings such as status epilepticus and tachycardia, hyper/hypotension, and progress to multi-organ failure. There are clues that gastric lavage and administration of activated charcoal may be beneficial to patients. As reported by Emir *et al.*, a 22-years-old female patient received 18000 mg of ALA, but activated charcoal was administered within 2 hours and she was discharged healthy after 3 days of intensive care [5]. Supportive treatment has been used in all of them. Six of the 7 cases were given diazepam, midazolam, phenytoin, clonazepam, phenobarbitone, levetiracetam, and lorazepam for convulsion treatment in the intensive care unit [5-11]. Despite those anticonvulsants, refractory convulsions have been controlled with thiopental sodium in one patient and propofol in another patient [9, 11]. We could control the refractory convulsion with ketamine infusion in our case. There is no known direct antidote for ALA toxication. However, in the study of Martin E. GAL (1965), the mortality rate was found to be lower in rats that were given toxic doses of ALA together with thiamine (Vitamin B1) compared to those who were not given (0% vs 75%) [15]. Since cases presenting with ALA toxication are noisy, Brain Computed Tomography (CT) was performed in most cases and Brain Magnetic Resonance Imaging (MRI) was performed in one case to exclude intracranial pathology. However, all of them were normal [5, 8-11].

The reason that ALA causes neurological symptoms has been attributed to its ability to easily cross the blood-brain barrier [5, 16]. In some cases, reported previously, lactate was found high, as in our case [6, 7, 11]. In a study conducted in the rhesus monkey liver, they shown that high-dose intravenous ALA caused edema and deterioration in vital membranes in mitochondria. [12] We can explain it as the inadequate oxidative phosphorylation as a result of the damage to the mitochondria and the conversion of the produced pyruvic acid to lactate.

Data on chronic intoxication of ALA are also rare. Ridruejo *et al.* reported ALA-induced Acute Cholestatic Hepatitis in a 63-years-old case, but they did not report a hypothesis about its pathogenesis [17]. As can be seen in Table 1, liver function tests (LFT) (AST, ALT) were increased in our case. Similar findings have been seen in the previous studies [6, 10].

In the experimental monkey study, obvious structural deterioration in the liver was reported with the ALA toxicity [12]. The increase in INR in the cases is also remarkable [6, 7, 9]. In our case, the INR was high up to the 5th day and gastrointestinal bleeding was observed together. In the case of Hadzik *et al.*, it increased to 6.4 in the 7th hour. At the same time, their LFTs have increased 6 times. It is the only case of death in the literature [7].

Our case's EEG was normal at 20th days and 3rd months after his first admission. None of the previously reported cases have

EEGs taken in the acute period<sup>[8, 11]</sup>. Performing an EEG in the acute period with ALA intoxication may enable us to better understand the convulsion type of the cases.

## CONCLUSION

Adults should keep this drug in protected places. Children and adults with suspected ALA intake should be referred to a tertiary care institution as soon as possible. In the first step, gastric lavage and activated charcoal should be applied. Since ALA does not have a specific antidote, it should be prepared to deal with resistant convulsions, metabolic acidosis, and multi-organ failure in addition to general supportive treatment. New and multi-center studies are needed for the subject to be fully understood.

## Disclosure

Declarations of interest: None

## Conflict of Interest:

There is no conflict of interest between the authors who wrote this article.

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