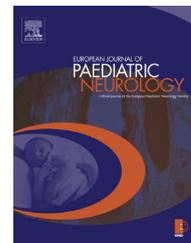




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Case Study

A rare cause of status epilepticus; alpha lipoic acid intoxication, case report and review of the literature



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ABSTRACT

Introduction: Alpha lipoic acid is a powerful antioxidant widely used for the supplementary treatment of diabetic neuropathy. Intoxication with alpha lipoic acid is very rare. There is no reported dose of safety in children.

Case report: A 14-month-old previously healthy girl was referred to our hospital with the diagnosis of drug intoxication. She was admitted to the emergency department with lethargy and continuing involuntary movements for several hours after she had ingested an unknown amount of alpha lipoic acid. On admission she was lethargic and had myoclonic seizures involving all extremities. She had no fever and laboratory examinations were normal except for mild metabolic acidosis. The seizures were unresponsive to bolus midazolam, phenytoin infusion and levetiracetam infusion. She was taken to the pediatric intensive care unit with the diagnosis of status epilepticus. After failure of the treatment with midazolam infusion she was intubated and thiopental sodium infusion was started. Her myoclonic seizures were controlled with thiopental sodium infusion. After 48 h intubation and mechanical ventilation thiopental sodium was gradually reduced and then stopped. Following the withdraw of thiopental sodium, she was seizure free on her discharge on the 8th day.

Conclusion: Alpha lipoic acid and derivatives cause side effects in children like refractory convulsions. They are frequently rendered as vitamins by diabetic patients and are left at places where children can easily access them. Therefore, when faced with refractory convulsions in children who have had no disease before, intoxication by medicaments with alpha lipoic acid should be taken into consideration.

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1. Introduction

Alpha lipoic acid (ALA), also known as thioctic acid, is a cofactor found in a number of multienzyme complexes.^{1,2} Alpha-lipoic acid was first characterized by Reed et al., in 1951.³ Dietary supplementation with ALA has been utilized in hepatic disorders, imbalance of redox status such as ischemia–reperfusion, polyneuropathy, diabetes, hypertension.⁴ Alpha lipoic acid terminates free radicals, chelates transition metal ions, increases cytosolic glutathione and vitamin C levels. Alpha lipoic acid is a powerful antioxidant widely used for the supplementary treatment of diabetic neuropathy.^{1,2} It improves glycemic control and polyneuropathies associated with diabetes mellitus and can also be used in cases with heavy metal poisoning. It also demonstrates a wide and safe therapeutic range in adults.^{5,6} The intoxication is very rare, the increased risk of gastrointestinal side effects (loss of appetite as well as a bitter taste in the throat when swallowing the capsules, nausea, vomiting) mostly associated with 1200 mg in adults and is well tolerated.^{5,6} Allergic skin reactions and possible hypoglycemia in diabetic patients with ALA doses over 2000 mg/day were also reported.⁵ There is no reported dose of safety in children.

2. Case report

Herein we report a 14-month-old previously healthy girl who referred to our hospital with the diagnosis of drug intoxication. She was admitted to the emergency department with lethargy and continuing involuntary movements for several hours after she had ingested an unknown amount of pills of 600 mg ALA belonging to a diabetic parent at home. Alpha lipoic acid was the only drug that had been found nearby the patient. There was no history of trauma or convulsion before. There was no history of epilepsy in her family. On admission she was lethargic, both pupils were mid-dilated with delayed pupillary reflex, bilateral extensor toe signs were present and had myoclonic seizures involving all extremities. Her blood pressure was 130/80 mmHg, heart rate was 172/minute and body temperature was 36.4 °C. The laboratory examinations were normal except for a mild metabolic acidosis (pH: 7.24, pCO₂: 44 mmHg, HCO₃⁻: 13.4 mmol/L, BE: -13.7 mmol/L) excluding an infectious disease or a systemic illness (Table 1). Toxicologic screening of urine for drugs such as amphetamines, benzodiazepines, barbiturates, methamphetamines, opiates, phencyclidine, tricyclic antidepressants, methadone, cannabinoid and benzococaine were negative. Cranial computed tomography was normal. The seizures were

unresponsive to bolus midazolam injection, phenytoin infusion at 20 mg/kg dose and levetiracetam infusion at 20 mg/kg dose. She was taken to the pediatric intensive care unit with the diagnosis of status epilepticus. After failure of the treatment with midazolam infusion (up to 1 mg/kg/hour) she was intubated and thiopental sodium infusion was started. Her myoclonic seizures was controlled with the thiopental sodium infusion (3 mg/kg/hour). After 48 h intubation and mechanical ventilation the thiopental sodium infusion was gradually reduced and then stopped. Following the withdrawal of the thiopental sodium infusion she was seizure free, levetiracetam continued as anticonvulsant drug and she was discharged at the 8th day.

As the patient was well and had no convulsions identified during the outpatient clinic controls, levetiracetam treatment was stopped. Electroencephalogram and cranial magnetic resonance imaging findings were normal.

3. Discussion

Alpha lipoic acid is most frequently used in diabetic neuropathy. Alpha lipoic acid is used both by clinicians and herbalists and can be obtained without prescription.^{7,8} It is frequently rendered as vitamins by diabetic patients and are left at places where children can easily access them.

Alpha lipoic acid demonstrates a wide and safe therapeutic range in adults.^{5,6} The intoxication is very rare, 1200 mg/day and 2000 mg/day doses are both well tolerated in adults.^{5,6} The oral dose at which 50% of the animals die after application of lipoic acid is 1130 mg/kg/day for rats and 502 mg/kg/day for mice.¹ High doses of ALA seems to be tolerated well in animal researches.^{1,9} There is no reported dose of safety in children. Alpha lipoic acid and derivatives cause side effects in children like refractory convulsions. With the best of our knowledge there are only three ALA intoxication cases occurred in childhood and reported in current literature.^{2,9,10} Refractory convulsions are seen in all cases. In one of the cases the patient had to be intubated and thiopental sodium infusion was required. In another case, convulsions could be stopped without using thiopental sodium infusion (Table 2). The first mortal case with alpha lipoic acid intoxication was reported in 2012.⁹ The patient was a 14-year-old girl who ingested a large amount of alpha-lipoic acid with suicidal intention.⁹ The patient died because of multiorgan failure within 24 h following the ingestion.

As diabetes mellitus and the frequency of diabetic neuropathy increase, possibility of ALA usage and intoxication in children living in the same house also rises. Neither the parents nor the physicians are aware of the toxicity of alpha-

Table 1 – Laboratory results.

Hb	Wbc	Plt	CRP	Glu	Ure	Cre	Na	K	Cl	Ca	AST	ALT	CK	Lac
11.6	24.5	295	0.4	188	14.6	0.38	138	3.6	107	9.4	37	22	231	23.3

Hb: hemoglobin (9.6–13.1 g/dl), Wbc: white blood cell (6,3–12,6 × 10³/mm³), Plt: platelet (214–459 × 10³/mm³), Glu: glucose (60–100 mg/dl), Ure: urea (16.6–48.5 mg/dl), Cre: creatinine (0.57–0.87 mg/dl), Na: sodium (136–145 mmol/L), K: potassium (3.5–5.1 mmol/L), Cl: chloride (98–107 mmol/L), Ca: calcium (9–11 mg/dL), AST: aspartate aminotransferase (10–48 U/L), ALT: alanine aminotransferase (10–48 U/L), CK: creatine kinase (0–190 IU/L), Lac: lactate (4.5–19.8 mg/dl).

Table 2 – Specificities of intoxication with alpha lipoic acid in literature.

	Age	Ingested drug amount	Endotracheal intubation	Thiopental sodium infusion	Intoxication type	Multiorgan failure	Mortality
Özçetin et al. 2012	10 months	Unknown amount	Yes	Yes	Accidental	No	No
Karaarslan et al. 2013	20 months	226 mg/kg	No	No	Accidental	No	No
Hadzik et al. 2014	14 year	Large amount	Yes	No	Non-accidental (suicide Attemption)	Yes ^a	Yes
Our patient	14 months	Unknown amount	Yes	Yes	Accidental	No	No

^a Multiorgan failure; decreased myocardial contractility, seizures, anuria, thrombocytopenia, and coagulopathy.

lipoic acid. When faced with refractory convulsions in children who have had no disease before, intoxication by medicaments with ALA should be taken into consideration.

This kind of medicaments has no safe dose for children and may lead even to death due to intoxication. Therefore requirements of sale, packaging and preservation at home should be improved.

Conflict of interest

None.

REFERENCES

- Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. *Gen Pharmacol* 1997;29:315–31.
- Karaarslan U, İşgüder R, Bağ Ö, Kışla M, Ağın H, Ünal N. Alpha lipoic acid intoxication, treatment and outcome. *Clin Toxicol (Phila)* 2013;51:522.
- Vigil M, Berkson BM, Garcia AP. Adverse effects of high doses of intravenous alpha lipoic acid on liver mitochondria. *Glob Adv Health Med* 2014;3:25–7.
- Moini H, Packer L, Saris NE. Antioxidant and prooxidant activities of alpha lipoic acid and dihydrolipoic acid. *Toxicol Appl Pharmacol* 2002;182:84–90.
- Porasuphatana S, Suddee S, Nartnampong A, Konsil J, Harnwong B, Santaweek A. Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alpha-lipoic acid: a randomized double-blinded placebo-controlled study. *Asia Pac J Clin Nutr* 2012;21:12–21.
- Hahn JR, Kim BJ, Kim KW. Clinical experience with thioctic acid (thioctic acid) in the treatment of distal symmetric polyneuropathy in Korean diabetic patients. *J Diabetes Complications* 2004;18:79–85.
- Hasan SS, Ahmed SI, Bukhari NI, Loon WC. Use of complementary and alternative medicine among patients with chronic diseases at outpatient clinics. *Complement Ther Clin Pract* 2009;15:152–7.
- Cicero AF, Derosa G, Gaddi A. What do herbalists suggest to diabetic patients in order to improve glycemic control? Evaluation of scientific evidence and potential risks. *Acta Diabetol* 2004;41:91–8.
- Hadzik B, Grass H, Mayatepek E, Daldrup T, Hoehn T. Fatal non-accidental alpha-lipoic acid intoxication in an adolescent girl. *Klin Padiatr* 2014;226:292–4.
- Özçetin M, Yılmaz R, Tetikçok R, Karaarslan E, Dürer Z, Narin B. Alpha lipoic acid intoxication in a 10 months old infant; a case report. *Anatol J Clin Investig* 2012;6:66–7.