Case Series

Journal of Veterinary Emergency and Critical Care **19**(5) 2009, pp 501–506
doi: 10.1111/j.1476-4431.2009.00460.x

Therapy and outcome of suspected alpha lipoic acid toxicity in two dogs

Erika G. Loftin, DVM and Lee V. Herold, DVM, DACVECC

Abstract

Objective – To report a suspected toxicity in 2 dogs; to discuss therapy and prognosis.
Series Summary – Suspected alpha lipoic acid (ALA) toxicity was diagnosed based on clinical history and compatible laboratory findings in 2 dogs. Case 1 was presented within 10 hours of ALA ingestion, with initial behavioral changes likely due to hypoglycemia. During the course of hospitalization, hypoglycemia persisted and evidence of acute hepatic insult developed. With aggressive supportive care (including IV fluids with dextrose supplementation, hepatoprotective medications, and a plasma transfusion), he made a full recovery. Case 2 was presented approximately 60 hours after ALA ingestion, and was found to be in oliguric renal failure. She was treated with IV fluids, gastroprotective medications, and furosemide, but her condition deteriorated and she was ultimately euthanized within 16 hours of admission to the hospital.
New or Unique Information Provided – ALA is an uncommon but serious toxin that should be considered in cases presenting with hypoglycemia, acute renal failure, or acute hepatic insult.

(J Vet Emerg Crit Care 2009; 19(5): 501–506) doi: 10.1111/j.1476-4431.2009.00460.x

Keywords: antioxidant, hepatic, hypoglycemia, lipoic acid, renal, toxin

Introduction

Alpha lipoic acid (ALA), also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid, is a naturally occurring compound that acts as a cofactor in many biologic systems. Biochemical and antioxidant characteristics of ALA have been described.[1,2] ALA has been investigated as a possible adjunctive treatment of various conditions including diabetes mellitus and associated complications,[3,4] cancer,[5] multiple sclerosis,[6] ischemia/reperfusion injury,[7] *Amanita* mushroom poisoning,[2] Alzheimer's disease and related dementias,[8] heavy metal toxicities (particularly arsenic),[9] and human immunodeficiency virus/acquired immune deficiency syndrome.[10] ALA is readily available over-the-counter (OTC) in various strengths in North America, and also in combination products with L-carnitine and other ingredients. Accidental ingestion or iatrogenic administrations are possible methods of exposure for veterinary patients.

ALA is thought to be very safe at the doses recommended for clinical use in humans. Rare adverse effects in humans include allergic skin conditions,[2,6] nausea and vomiting,[4] headaches,[6,11] and hypoglycemia in diabetic patients.[12,13] ALA is well absorbed by the oral route, though in humans, ALA has been shown to have limited bioavailability of about 30% due to hepatic first-pass metabolism.[11] There are few reports in the literature documenting ALA toxicity in domestic animals.[14,15] ALA has been reported to be 10 times more toxic in cats than in humans, dogs, or rats.[15] Toxicity in cats typically manifests with clinicopathologic findings consisting of reduced food intake, ataxia, hypersensitivity, hypersalivation, vomiting, or elevated hepatic enzymes and was reliably observed after a dose of 60 mg/kg. ALA doses of 30 mg/kg in cats were associated with mild acute hepatocellular damage observed histologically.[15] The maximal tolerated dose (MTD) was determined to be 13 mg/kg for a single oral dose, which is 1/10 to 1/40 of the MTD reported in other species.[15] In dogs, the MTD is 126 mg/kg[15] and an oral LD_{50} has been reported as 400–500 mg/kg.[2] A single case report of ALA ingestion by a German Shepherd dog has recently been published.[14] The dog in this report presented with hypoglycemia and associated clinical signs, and improved clinically with supportive care including dextrose continuous rate infusion (CRI), S-adenosyl methionine (SAM-E), and silymarin. The dog did not have changes in renal or hepatic biochemical parameters on initial evaluation and follow-up testing was not reported. The cases reported here describe the clinical

DoveLewis Emergency Animal Hospital, Portland, OR

Address correspondence and reprint requests to
Dr. Erika Loftin, DoveLewis Emergency Animal Hospital, 1945 NW Pettygrove St, Portland, OR 97209, USA.
Email: eloftin@dovelewis.org

presentation, management and outcome in 2 dogs with suspected ALA toxicity.

Case 1

A 1.5-year-old neutered male Greater Swiss Mountain dog, weighing 31.4 kg, was presented for evaluation approximately 7–10 hours after ingesting a nutritional supplement containing ALA. The product was described as Thioctic Acid D form (300 mg tablets), and the ingested dose was estimated to be 191 mg/kg. The patient began shaking, and became aggressive toward the other dogs in the home. Before presentation the owner administered oral corn syrup as recommended by a poison control center. On initial examination, the dog was ambulatory and appeared very excitable. He was panting, normothermic (39°C [102°F]) and tachycardic (180/min). Systolic blood pressure was 100 mm Hg. Hydration was adequate, and no other significant abnormalities were noted on examination.

Blood glucose was measured on a hand-held glucometer[a] on initial triage, and was 2.8 mmol/L (50 mg/dL) (reference interval, 4.1–7.9 mmol/L [74–143 mg/dL]). Initial diagnostic testing included a CBC, and biochemical profile. Abnormalities on the biochemistry panel (see Table 1) included mildly elevated alanine aminotransferase (ALT, 170 U/L; reference interval, 5–107 U/L), elevated albumin (48 g/L [4.8 g/dL]; reference interval, 23–40 g/L [2.3–4.0 g/dL]) and elevated lipase (3865 IU/L; reference interval 200–1800 IU/L). Electrolytes were within their reference intervals. The CBC demonstrated hemoconcentration with elevated PCV and total plasma protein at 65% and 80 g/L (8.0 g/dL), respectively (reference intervals, 37–55% and 52–78 g/L [5.2–7.8 g/dL], respectively). The remainder of the CBC was within reference intervals.

The dog was sedated with butorphanol[b] (0.32 mg/kg, IV) to allow IV catheter placement. He was treated with 60 mL of 25% dextrose (1.8 mL/kg, IV), following which the blood glucose was 9.9 mmol/L (178 mg/dL). He was treated with a balanced isotonic crystalloid[c] containing 1.25% dextrose (4.8 mL/kg/h) to maintain hydration and provide diuresis, as well as SAM-E[d] (21.5 mg/kg, PO, q 24 h) for hepatoprotection.

On Day 2 of hospitalization, the physical examination was unremarkable. Blood glucose was too low to register (<1.1 mmol/L [20 mg/dL]); the dog was given another bolus of 25% dextrose (1.1 mL/kg, IV), and supplementation was increased to 2.5% in his IV fluids. The dog's appetite was poor. After IV fluids were inadvertently discontinued for a short time, he was again noted to be hypoglycemic (1.9 mmol/L [38 mg/dL]), and an additional bolus of 25% dextrose (1.1 mL/kg, IV) was given. Blood glucose monitoring was continued every 2–4 hours throughout the day, and the patient remained hypoglycemic (3.1 mmol/L [55 mg/dL]); however, he demonstrated no clinical signs of hypoglycemia. Limited diagnostic testing (see Table 1) revealed elevations in creatinine (177 μmol/L [2.0 mg/dL]; reference interval, 44–159 μmol/L [0.5–1.8 mg/dL]), total bilirubin (37.6 μmol/L [2.2 mg/dL]; reference interval 0–6.8 μmol/L [0–0.4 mg/dL]), and ALT (>1000 U/L; reference interval 5–107 U/L), as well as hypokalemia (3.3 mmol/L; reference interval 3.5–5.8 mmol/L). PCV was 54% and TPP was 60 g/L (6.0 g/dL). A urinalysis was performed, and revealed a specific gravity of 1.032, 4–6 transitional cells per high-power field, and no casts. IV fluids were increased to 6.4 mL/kg/h for additional

Table 1: Trends in selected biochemical values during and after hospitalization in Case 1

Biochemical parameter	Reference interval	Day 1	Day 2	Day 3	Day 4	Day 7
ALT	5–107 U/L	170	↑	↑	4923	4078
ALP	10–150 U/L	124	NA	NA	564	845
AST	5–55 U/L	NA	NA	NA	510	100
GGT	0–14 U/L	NA	NA	NA	17	39
Bili	0–6.8 μmol/L	8.5	37.6	60	130	18.8
Bili	0.0–0.4 mg/dL	0.5	2.2	3.5	7.6	1.1
Creatinine	44–159 μmol/L	150	177	168	NA	159
Creatinine	0.5–1.8 mg/dL	1.7	2.0	1.9	NA	1.8
BUN	2.5–9.6 mmol/L	7.9	NA	NA	5	5.7
BUN	7–27 mg/dL	22	NA	NA	14	16
Albumin	23–40 g/L	48	NA	NA	29	34
Albumin	2.3–4.0 g/dL	4.8	NA	NA	2.9	3.4
Glucose	4.1–7.9 mmol/L	2.8	3.1	3.3	5	5.7
Glucose	74–143 mg/dL	50	55	60	90	103

↑ Numerical value is unable to be read due to the value being higher than the upper reading range of the chemistry analyzer.
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ glutamyltransferase; Bili, total bilibrubin; BUN, blood urea nitrogen; NA, not analyzed.

diuresis due to the elevated creatinine and urine specific gravity, and vitamin B complex[e] (2 mL/L) and potassium chloride[f] (30 mEq/L) were added to the IV fluids. He had a single episode of regurgitation, and was administered metoclopramide[g] (0.2 mg/kg, SQ, once, then 2 mg/kg/d, CRI).

On Day 3, physical examination findings were unchanged, and the dog was eating small amounts. Silymarin[h] (16 mg/kg, PO, q 12 h) was added for additional hepatoprotection. Blood glucose was monitored every 8 hours, and hypoglycemia was repeatedly documented (2.8–3.4 mmol/L [50–62 mg/dL]). Clotting time was found to be prolonged; prothrombin time (PT) was 38 seconds (reference interval, 9–12 s) and activated partial thromboplastin time (PTT) was 99 seconds (reference interval, 59–87 s). Recheck laboratory values (see Table 1) revealed normal electrolytes, persistent ALT elevation (>1,000 U/L), progressive total bilirubin elevation (60 μmol/L [3.5 mg/dL]), persistent mild creatinine elevation (168 μmol/L [1.9 mg/dL]). The PCV was 54% and TPP was 52 g/L (5.2 g/dL). The coagulopathy was treated with 1 U (300mL, 9.5 mL/kg) type DEA 1.1 negative fresh frozen plasma. Posttransfusion coagulation testing was improved (PT, 17 s; PTT, 87 s).

On Day 4, the dog was started on vitamin K_1[i] (1.6 mg/kg, PO, q 24 h) as additional therapy for his coagulopathy. He remained hypoglycemic (2.7–3.1 mmol/L [49–56 mg/dL]). A liver chemistry profile was submitted to a reference laboratory (see Table 1), and revealed a progressive elevation in his total bilirubin (130 μmol/L [7.6 mg/dL]; reference interval, 0–6.8 μmol/L [0–0.4 mg/dL]) and liver enzymes including alkaline phosphatase (546 U/L; reference interval, 10–150 U/L), ALT (4923 U/L; reference interval, 5–107 U/L), aspartate aminotransferase (510 U/L; reference interval, 5–55 U/L), and γ glutamyltransferase (17 U/L; reference interval, 0–14 U/L). Hepatic synthetic parameters blood urea nitrogen, cholesterol, albumin, and glucose were within normal limits. A platelet count was within the reference interval (210×10^9/L; reference interval $164–510 \times 10^9$/L). He was prophylactically started on lactulose[j] (426 mg/kg, PO, q 12 h) due to potential risk for development of hepatic encephalopathy. Further hospitalization was declined due to financial limitations of the owner. The dog was discharged on silymarin (31.8 mg/kg, PO, q 12 h), SAM-E (21.5 mg/kg, PO, q 24 h), vitamin K_1 (1.6 mg/kg, PO, q 24 h), and lactulose (426 mg/kg, PO, q 12 h), with instructions to recheck with the referring veterinarian the following morning for continued IV fluid therapy and supportive care.

Recheck biochemical and coagulation profiles (see Table 1) were obtained by the referring veterinarian 3 days after discharge (Day 7 from time of hospital admission), and continued to demonstrate marked liver enzyme elevations (ALT, 4078 U/L; reference interval, 5–107 U/L; alkaline phosphatase, 845 U/L; reference interval, 10–150 U/L; aspartate aminotransferase, 100 U/L; reference interval, 5–55 U/L; and γ glutamyltransferase, 49 U/L; reference interval 0–14). Total bilirubin and creatinine were improved, but remained mildly elevated (total bilirubin 18.8 μmol/L [1.1 mg/dL]; reference interval, 0–6.8 μmol/L [0–0.4 mg/dL]; creatinine, 159 μmol/L [1.8 mg/dL]; reference interval, 44.2–159.1 μmol/L [0.5–1.8 mg/dL]); normoglycemia was noted (5.7 mmol/L [103 mg/dL]). PT and PTT were within reference intervals (PT, 9.4; reference interval, 6–12 s and PTT, 17.1; reference interval, 10–25 s). According to the owner, the dog was clinically normal at home with a good appetite and no vomiting or diarrhea. Further follow-up lab work was declined, but a phone update approximately 4 months after discharge revealed that the patient was asymptomatic.

Case 2

A 3.5-year-old spayed female American Staffordshire Terrier, weighing 23.9 kg, ingested approximately 50 ALA 100 mg gel tabs (estimated dose 210 mg/kg). The owner noted that she seemed weak and lethargic the evening of ingestion, and also vomited multiple times. She continued to vomit and refuse food, and was presented to an emergency clinic 2.5 days after ingestion. At the time of initial examination, she was hypothermic (37°C [98.7°F]), pulse rate was 130/min, and respiratory rate was 30/min. She was estimated to be 7–8% dehydrated based on prolonged skin turgor and tacky mucous membranes. She was painful on abdominal palpation; no bladder was palpable. Systolic blood pressure was 104 mm Hg. She was noted to have melena on rectal examination. The remainder of the physical examination was unremarkable.

Initial diagnostic testing included a CBC, which was within the reference intervals, and a serum biochemical profile. The chemistry profile revealed hyponatremia (133 mmol/L; reference interval, 144–160 mmol/L), hyperkalemia (6.6 mmol/L; reference interval, 3.5–5.8 mmol/L), hypochloremia (95 mmol/L; reference interval, 109–122 mmol/L), elevated ALT (687 U/L; reference interval 10–100 U/L), elevated blood urea nitrogen (123.9 mmol/L [347 mg/dL]; reference interval, 2.5–9.6 mmol/L [7–27 mg/dL]), elevated creatinine (707 μmol/L [8.0 mg/dL]; reference interval, 44.2–159.1 μmol/L [0.5–1.8 mg/dL]), hyperphosphatemia (8 mmol/L [24.7 mg/dL]; reference interval, 1.8–2.2 mmol/L [5.5–6.8 mg/dL]), hypoglobulinemia (24 g/L [2.4 g/dL], reference interval, 25–45 g/L [2.5–4.5 g/dL]), and elevated lipase (4097 U/L; reference interval, 200–1800 U/L). Blood glucose was

normal (7.3 mmol/L [131 mg/dL]; reference interval, 4.1–7.9 mmol/L [74–143 mg/dL]). Urine was not obtained initially. Because of limited financial resources and strong suspicion for ALA toxicity, the owner declined additional diagnostic testing including bacteriologic culture and susceptibility testing of the urine, abdominal imaging, leptospirosis serology, and adrenocorticotrophic hormone stimulation test.

An IV catheter was placed, and she was initially started on a balanced isotonic crystalloid[k] (4.6 mL/kg/h). She was treated with dolasetron[l] (0.63 mg/kg, IV, q 24 h), buprenorphine[m] (0.01 mg/kg, IV, q 8 h), and famotidine[n] (0.5 mg/kg, IV, q 24 h). She was scheduled to receive carafate[o] (1 g, PO, q 8 h), and oral hepatoprotective medications including SAM-E (18.8 mg/kg, PO, q 24 h), silymarin (20.9 mg/kg, PO, q 24 h), and N-acetylcysteine[p] (134.7 mg/kg PO once, then 67.4 mg/kg, PO, q 6 h) following control of emesis. Shortly after admission to the hospital, her IV fluid rate was increased to 16.7 mL/kg/h to more rapidly achieve rehydration and provide diuresis.

Electrolytes were rechecked approximately 8 hours after admission to the hospital, and revealed continued hyponatremia (136 mmol/L), hyperkalemia (6.3 mmol/L), and hypochloremia (94 mmol/L). The dog was noted to urinate in the afternoon, but the volume was not quantified. Through the course of hospitalization, hypothermia worsened (37.9°C, [96.7°F]), and vomiting continued; therefore, oral medications could not be started. She was given furosemide[q] (4 mg/kg, IV) due to suspected oliguria and possible fluid overload (tachypnea, abdominal distension). Mild hypertension developed in the evening (systolic blood pressure 153 mm Hg, diastolic blood pressure 82 mm Hg, mean arterial pressure 111 mm Hg). Central venous pressure measurements would have been useful in predicting fluid tolerance, but were not possible due to financial limitations. She continued to decline clinically, and was euthanized. Necropsy revealed free abdominal fluid and extensive tissue edema. Histopathology of liver revealed acute passive congestion with mild diffuse fatty changes and concurrent mild portal hepatitis and fibrosis. Histopathology of kidney revealed diffuse marked acute proximal convoluted tubular epithelial degeneration and necrosis. No significant inflammation was noted in the renal tissue. The adrenal glands were not submitted for histopathology, but appeared grossly normal.

Discussion

ALA has been extensively investigated in human medicine as a component of therapy for a multitude of conditions ranging from diabetic polyneuropathy to Alzheimer's disease.[2,4–10] ALA is readily available OTC, where it is primarily marketed as an antioxidant. Although ALA has been recommended for treatment of various diseases in veterinary patients including diabetes mellitus,[14,16] peripheral neuropathy,[16] cataracts, [16] glaucoma,[16] and cognitive dysfunction,[16] there is a paucity of information in the veterinary literature regarding the potentially serious consequences of ALA toxicity. No information was located upon review of 2 veterinary toxicology texts.[17,18] Clinical signs of toxicity in dogs can include vomiting, ataxia, hypersalivation, tremors, seizures, and weakness.[14] Hepatic failure and acute renal failure can occur.[14] There is no specific antidote for ALA toxicity; therapy remains symptomatic and supportive.

The American Society for the Prevention of Cruelty to Animals Poison Control Center recommends decontamination at doses >5 mg/kg (cats) or >50 mg/kg (dogs), ideally within an hour of ingestion. Other current recommendations include control of hypoglycemia, correction of dehydration and vomiting, and treatment of tremors or seizures. Hepatoprotective medications (eg, SAM-E, N-acetylcysteine, silymarin) are recommended though their efficacy has not been determined. Fluid diuresis is recommended to reduce the risk of acute renal failure. Placement of an indwelling urinary catheter should be recommended in patients presenting with azotemia, to ensure adequate urine output and early intervention if there is any evidence of oliguria. Hemodialysis or continuous renal replacement therapy may be necessary if oliguria does not respond to fluid therapy and diuretics. Thiamine deficiency has been shown to exacerbate toxic effects of ALA in a rat model, and concurrent intraperitoneal injection of thiamine along with ALA in thiamine-deficient rats protected them from toxicity.[19] The benefit of thiamine supplementation in dogs without thiamine deficiency is unknown; however, thiamine supplementation may reduce toxic effects of ALA and has limited adverse effects.

ALA has several actions that result in hypoglycemia, including increased glucose uptake, increase in the number of glucose-transport proteins, increased glycogen synthesis, inhibition of gluconeogenesis, and providing a cofactor for enzymatic oxidization of glucose in the mitochondria.[12,20] ALA also improves endothelial function, leading to improvement in capillary blood flow and therefore increased delivery of the glucose substrate to muscle tissue.[20] Differential diagnoses for hypoglycemia should include other medications or toxins (eg, sulfonylurea oral antihyperglycemic agents, insulin, xylitol), as well as insulinoma, hypoadrenocorticism, parasitism, liver failure, and sepsis. Although point-of-care glucometers tend to underesti-

mate blood glucose concentrations,[21] hypoglycemia was persistently demonstrated in Case 1 despite CRI dextrose supplementation. Hypoglycemia in this patient may have been the result of increased glucose uptake and utilization by activation of insulin signaling pathways. Hepatic failure was unlikely to have contributed to hypoglycemia in Case 1, as hypoglycemia was documented early in the course of toxicosis without concurrent evidence of hepatic failure. Insulin autoimmune syndrome (IAS) has been documented rarely in humans taking ALA.[13] This syndrome is characterized by frequent hypoglycemic episodes associated with the presence of autoantibodies to insulin in humans who have not received insulin injections. Insulin autoimmune syndrome has not been documented in veterinary patients, and was unlikely to have contributed hypoglycemia in Case 1. Case 2 did not demonstrate hypoglycemia; however, the late presentation 2.5 days after ingestion may have been a factor in our inability to document the hypoglycemic stage of toxicity.

The renal toxicity produced by ALA has not been investigated. In fact, ALA has been shown to be helpful for protection against renal ischemic-reperfusion injury,[7] as well as being protective against vancomycin,[22] gentamicin,[23] adriamycin,[24] and cisplatin[25] induced nephrotoxicity in rats. ALA has been administered in human subjects with severe kidney damage and end-stage renal disease without further deterioration of renal parameters.[26] Differences in species sensitivity, metabolism, and excretion of ALA may play a role in renal toxicity. Renal injury may be the result of prolonged hypoglycemia and hypovolemia (secondary to emesis and decreased intake) leading to hypotension and reduced renal blood flow. Case 1 had mild increases in creatinine that were likely secondary to prerenal mechanisms including dehydration. Case 2 had biochemical changes supportive of acute renal failure and was suspected to have developed oliguric renal failure. Renal histopathology from Case 2 revealed acute proximal tubular epithelial degeneration and necrosis. These histopathologic changes are not specific for ALA toxicity, but rather may represent ischemic injury to the kidneys as the S3 segment of the proximal tubule is highly susceptible to hypoxic damage due to its high metabolic rate. Differential diagnoses for acute renal failure should include toxins (eg, NSAIDS, ethylene glycol, grapes or raisins in dogs, lilies in cats), leptospirosis, pyelonephritis, ureteral obstruction, hypotensive episode, or neoplasia. Unfortunately further diagnostic testing for renal failure was not performed due to financial restrictions of the client.

Hepatotoxicity of ALA in these 2 cases was supported by hepatic enzyme elevations. The mechanism of hepatotoxicity in ALA is not known. The antioxidant properties of ALA have been well characterized, but ALA and its metabolites have also been postulated to have pro-oxidant effects, and may modulate biologic processes via oxidation of cellular proteins.[1] Hepatic histopathology in cats with ALA toxicity demonstrated swollen, granular to vesicular cytoplasm of the centrilobular regions of the liver.[15] Hepatic histopathology in rats administered high doses of ALA was characterized by centrilobular hypertrophy.[27] Hepatic histopathology in Case 2 demonstrated acute passive congestion more accentuated in the centrilobular region as well as some mild fatty change, and mild portal hepatitis and fibrosis. Although there was no historical evidence to support preexisting liver disease in a young patient, the histopathology results of portal inflammation and fibrosis may have represented previous hepatic dysfunction. Differential diagnoses for acute hepatic insult should include other toxins (eg, *Amanita* mushrooms, xylitol, sago palms, aflatoxicosis), sepsis, leptospirosis, salmonellosis, and anaphylaxis. Both hepatocellular and cholestatic liver enzymes were progressively elevated throughout hospitalization in Case 1. They remained elevated after discharge despite resolution of clinical signs and initiation of hepatoprotective medications early in the course of treatment. Hepatic function testing with bile acids, serum ammonia, and hepatic histopathology from Case 1 may have helped to further characterize the hepatotoxicity caused by ALA.

Case 1 had prolonged coagulation times (PT and PTT). Although serum bile acids were not performed, there was no other biochemical evidence of hepatic failure and it is uncertain whether PT and PTT elevations were a result of acute hepatic toxicity, or secondary to clotting factor consumption. In 1 cat that died acutely after a 60 mg/kg dose of ALA, hepatic histopathology revealed severe hepatic congestion and pulmonary thromboemboli.[15] The role of acute ALA toxicity in inducing hypercoagulobility, or DIC, and subsequent hypocoagulobility is not known. Plasma administration in Case 1 improved coagulation parameters. Coagulation was not assessed in Case 2.

Although both patients ingested similar doses of ALA, several possibilities may account for the difference in outcome. Case 1 was presented relatively early after ingestion and therapy including activated charcoal, fluid diuresis, and dextrose supplementation was begun soon after admission. Early therapy may have prevented further absorption of the ALA and protected the liver and kidneys from the consequences of hypotension and dehydration. The clinical syndrome in Case 1 was largely of hepatic injury and elevation of hepatic enzymes, whereas Case 2 demonstrated acute renal failure. The acute renal failure seen in Case 2 was likely

exacerbated by the dehydration resulting from prolonged vomiting and inappetance from the time of ingestion of the ALA through the time of presentation to the hospital. Differences in individual sensitivity to this toxin may also play a role in the differences in clinical syndrome and outcome. Ingestion of other substances should be considered, although the histories in both cases did not suggest other toxin exposure. The exact product could only be confirmed for Case 2; this product contained exclusively ALA, with no additional active ingredients. Further diagnostics (such as toxin assays and adrenocorticotrophic hormone stimulation testing) would have strengthened the diagnosis in both cases. Measurement of serum ALA levels would also be useful, both to confirm the diagnosis and to more accurately define the toxic and lethal doses.

In conclusion, ALA is a serious and possibly lethal toxin for small animal patients. Because of the expanding use in human medicine, and the easy OTC availability, it is likely that the exposure of veterinary patients will increase. Of concern, many clients may not consider ALA as either a potential toxin, or a true medication when questioned about possible exposures. The clinician must have an index of suspicion for ALA ingestion in cases presenting with acute hypoglycemia or renal or hepatic insult, and question owners specifically regarding possible exposure. There appears to be a wide range of species and individual sensitivity to this product, and larger case series may allow a better assessment of prognostic indicators, toxic/lethal dose, and the most effective therapeutic options.

Footnotes

[a] Elite XL hand-held glucometer, Bayer Healthcare, Elkhart, IN.
[b] Butorphanol (Torbugesic), FortDodge Animal Health, Fort Dodge, IA.
[c] Plasmalyte A, Baxter Healthcare Corp, Deerfield, IL.
[d] SAM-E (Denosyl), Nutramax Labs Inc, Edgewood, MD.
[e] Vitamin B complex, Vedco, St Joseph, MO.
[f] Potassium chloride, Hospira Inc, Lake Forest, IL.
[g] Metoclopramide (Reglan), Hospira Inc, Chicago, IL.
[h] Silymarin (milk thistle), US Nutrition Inc, Bohemia, NY.
[i] Vitamin K1 (VetaK1), Bimeda Inc, Riverside, MO.
[j] Lactulose (Enulose), Actavis MidAtlantic LLC, Baltimore, MD.
[k] Normasol-R, Abbott Laboratories, North Chicago, IL.
[l] Dolasetron (Anzemet), Aventis Pharmaceuticals Inc, Bridgewater, NJ.
[m] Buprenorphine (Buprenex), Bedford Laboratories, Bedford, OH.
[n] Famotidine (Pepcid), Baxter Healthcare Corp.
[o] Carafate (Sucralfate), LeVista Inc, Huntington, NY.
[p] N-acetylcysteine (Mucomyst), Hospira Inc.
[q] Furosemide (Lasix), Vedco.

References

1. Moini H, Packer L, Saris NL. Antioxidant and prooxidant activities of α-Lipoic acid and dihydrolipoic acid. Toxicol Appl Pharmacol 2002; 182:84–90.
2. Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. Free Radic Biol Med 1995; 19:227–250.
3. Packer L, Kraemer K, Rimbach G. Molecular aspects of lipoic acid in the prevention of diabetes complications. Nutrition 2001; 17(10): 888–895.
4. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy. Diabetes Care 2006; 29(11):2365–2370.
5. Wenzel U, Nickel A, Daniel H. α-lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant $O_2^{-\bullet}$-generation. Apoptosis 2005; 10:359–368.
6. Yadav V, Marracci G, Lovera J, et al. Lipoic acid in multiple sclerosis: a pilot study. Multiple Sclerosis 2005; 11:159–165.
7. Sehirli O, Sener E, Centinel S, et al. α-Lipoic acid protects against renal ischaemia-reperfusion injury in rats. Clin Exp Pharmacol Physiol 2008; 35:249–255.
8. Holmquist L, Stuchbury G, Berbaum K, et al. Lipoic acid as a novel treatment for Alzheimer's disease and related dementias. Pharmacol Ther 2007; 113:154–164.
9. Grunert RR. The effect of DL-α-lipoic acid on heavy-metal intoxication in mice and dogs. Arch Biochem Biophys 1960; 86:190–194.
10. Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. Klin Wochenschur 1991; 69:722–724.
11. Teichert J, Hermann R, Ruus P, et al. Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers. J Clin Pharmacol 2003; 43:1257–1267.
12. Khamaisi M, Rudich A, Potashnik R, et al. Lipoic acid induces hypoglycemia in fasting nondiabetic and diabetic rats. Metabolism 1999; 48(4):504–510.
13. Takeuchi Y, Miyamoto T, Kakizawa T, et al. Insulin autoimmune syndrome possibly caused by alpha lipoic acid. Intern Med 2007:237–239.
14. Means C. Ataxia and v omiting in a German Shepherd. NAVC Clinician's Brief 2008; 6(9):31–33.
15. Hill AS, Werner JA, Rogers QR, et al. Lipoic acid is 10 times more toxic in cats than reported in humans, dogs or rats. J Anim Physiol Anim Nutr 2004; 88:150–156.
16. Wynn SG, Marsden S. Manual of Natural Veterinary Medicine, 2nd edn. St Louis: Mosby Inc; 2003, p. 236, 480, 500, 510, 511.
17. Peterson ME, Talcott PA. Small Animal Toxicology, 2nd edn. St Louis: Elsevier Saunders; 2006.
18. Gupta RC. Veterinary Toxicology. New York: Elsevier Inc; 2007.
19. Gal EM. Reversal of selective toxicity of (-)-α-lipoic acid by thiamine in thiamine-deficient rats. Nature 1965; 207:535.
20. Jacob S, Rett K, Henriksen EJ, et al. Thioctic acid – effects on insulin sensitivity and glucose-metabolism. BioFactors 1999; 10: 169–174.
21. Wess G, Reusch C. Evaluation of five portable blood glucose meters for use in dogs. J Am Vet Med Assoc 2000; 216(2):203–209.
22. Celik I, Cihangiroglu M, Ilhan N, et al. Protective effects of different antioxidants and amrinone on vancomycin-induced nephrotoxicity. Basic Clin Pharmacol Toxicol 2005; 97:325–332.
23. Sandhya P, Mohandass S, Varalakshmi P. Role of DL α-lipoic acid in gentamicin induced nephrotoxicity. Mol Cell Biochem 1995; 145:11–17.
24. Malarkodi KP, Balachandar AV, Varalakshmi P. Protective effect of lipoic acid on adriamycin induced lipid peroxidation in rat kidney. Mol Cell Biochem 2003; 247:9–13.
25. Somani SM, Husain K, Whitworth C, et al. Dose-dependent protection by lipoic acid against cisplatin-induced nephrotoxicity in rats: antioxidant defense system. Pharmacol Toxicol 2000; 86:234–241.
26. Teichert J, Tuemmers T, Achenbach H, et al. Pharmacokinetics of Alpha-Lipoic acid in subjects with severe kidney damage and end-stage renal disease. J Clin Pharmacol 2005; 45:313–328.
27. Cremer DR, Rabeler R, Roberts A, Lynch B. Safety evaluation of α-lipoic acid (ALA). Regul Toxicol Pharmacol 2006; 46:29–41.