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VETERINARY TOXICOLOGY

# Hypoglycemia Associated With Oleander Toxicity in a Dog

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**Abstract** Oleander poisoning typically results in cardiac arrhythmias, hyperkalemia, and gastrointestinal irritation, and can be fatal. Oleander extracts have also been studied experimentally as hypoglycemic agents. Here, we describe a dog with confirmed oleander toxicosis presenting with classical symptoms and also hypoglycemia. After excluding other likely causes of hypoglycemia, the finding was attributed to oleander toxicosis, which has not been previously reported in dogs. A 7-year-old female spayed Maltese was presented to the emergency service after ingesting oleander leaves. Toxicosis was confirmed by measurement of digoxin using a competitive binding immunoassay, patient level 0.7 ng/mL (0.9 nmol/L) 24-h post-ingestion. Clinical symptoms included vomiting, cardiac arrhythmia, mild hyperkalemia, and hypoglycemia. Treatment was successful with aggressive supportive care, and the dog was discharged from the hospital after 48 h and made a full recovery. This case reviews the presentation and treatment of oleander toxicity but also highlights possible effects of oleander on blood sugar in dogs. Hypoglycemia in this dog, attributed to oleander poisoning, is interesting as it supports experimental research into hypoglycemic properties of oleander extracts.

**Keywords** Oleander · Hypoglycemia · Veterinary toxicology · Plant toxicity · Canine

## Introduction

Nerium oleander is an evergreen ornamental flowering shrub of the family Apocyanaceae. All parts of the plant are toxic, and the toxicity is due to toxic cardenolides [1]. These compounds are cardiac glycosides, and cause inhibition of plasmalemma $Na^+$,$K^+$ATPase [1]. The resulting effects in humans and animals are similar [2, 3] with gastrointestinal irritation, hyperkalemia, and cardiac arrhythmias, the predominant symptoms. In addition, renal damage has been noted in horses with oleander toxicosis [4].

Nerium oleander plant extracts have been under investigation as hypoglycemic agents in the study of diabetes mellitus in experimental animal models [5, 6]. In an experimental rat model, Mwafy and Yassin (2011) [5] demonstrated lower blood glucose levels in diabetic rats treated with Nerium oleander extract compared with controls. In another study [6], experimentally induced diabetic rats had improved pancreatic beta cell function when administered Nerium oleander distillate, suggesting insulin secretagogue and sensitizing effects of the extract. Further analysis by spectrometric analysis [7] has identified chlorogenic acid in Nerium leaves, a non-competitive inhibitor of alpha-glucosidase. In in vivo [7] rat models, chlorogenic acid suppressed the post-prandial rise in blood glucose and inhibited absorption of glucose from rat intestine in vitro [7].

Hypoglycemia has not been previously documented as a sequelae to Nerium oleander toxicosis. In this case report, we describe the successful treatment of a dog with documented oleander toxicosis, with hypoglycemia as a pertinent clinical finding.

## Case Presentation

A 7-year-old female spayed, 2.4-kg Maltese was evaluated at the VCA All-Care Animal Referral Center Emergency Service approximately 24 h after ingestion of an unknown amount of Nerium oleander leaves. Shortly after ingesting the leaves, the dog began vomiting multiple times and was taken to her regular veterinarian. A CBC and biochemical screen

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revealed leucocytosis, hyperphosphatemia, elevated blood urea nitrogen (BUN), low normal glucose, and high normal potassium (WBC 19.7 $10^3$/mm$^3$ [19.7 $10^9$/L], reference interval 6–17 $10^3$/mm$^3$ [6–17 $10^9$/L]; phosphorous 9.9 mg/dL [3.2 mmol/L], reference interval 2.9–6.6 mg/dL [0.9–2.1 mmol/L]; BUN 60 mg/dL [21.4 mmol/L], reference interval 7–25 mg/dL [2.5–8.9 mmol/L]; glucose 80 mg/dL [4.4 mmol/L], reference interval 75–116 mg/dL [4.2–6.4 mmol/L]; potassium 5.8 mmol/L, reference interval 3.7–5.8 mmol/L). Subcutaneous lactated Ringer's solution (250 mL) and maropitant (2 mg, SC) were administered, and the dog was released to the care of the owner. After continued vomiting and collapse at home, the dog was taken to a local emergency clinic. The dog was treated with lactated Ringer's solution (250 mL, IV), maropitant (2 mg, SC), and ampicillin (62.5 mg, SC). A repeat CBC and biochemical screen demonstrated potassium at the high end of normal with normalization of other values (potassium 5.6 mmol/L, reference interval 3.7–5.8 mmol/L). Due to worsening clinical signs, the dog was referred by the family veterinarian to the VCA All-Care Animal Referral Center for further evaluation and treatment.

Upon presentation, the dog was weakly ambulatory with depressed mentation and ataxia in the hind limbs. Initial physical examination revealed a pronounced bradyarrhythmia, with prolonged pauses and an average heart rate of 80 beats per minute. ECG showed second-degree AV block, type 1 with a variable heart rate. Abdominal palpation resulted in pain, nausea, and vomiting. Respiration and lung sounds were within normal limits. Initial radiographs of the chest and abdomen demonstrated subcutaneous emphysema thought to be iatrogenic secondary to subcutaneous fluid administration. Mild alveolar pulmonary lung pattern of the right cranial and middle lung lobes was attributed to recumbent atelectasis. Fluid distension of the stomach and small intestines suggested functional ileus. Granular material in the colon indicated dietary indiscretion. It was suspected that the clinical signs were a result of oleander toxicosis; however, to be thorough, an ACTH stimulation test was performed to rule out hypoadrenocorticism, and a digoxin level was performed. Due to ongoing nausea, a constant rate infusion of metoclopramide was initiated (62.5 mcg/kg/h), along with dolasetron (0.6 mg/kg IV) and famotidine (1 mg/kg IV). Normal saline (0.9 %) was administered at 2.5 mL/kg/h. Telemetry monitoring revealed frequent second degree heart block over the next 24 h with variable rate. Echocardiogram was within normal limits. Abdominal ultrasound showed fluid in the stomach and duodenum and no other abnormal findings. Results of ACTH stimulation were elevated, interpreted as a stress response for a sick patient (cortisol pre-administration of cosyntropin 15.9 μg/dL [438.7 nmol/L], reference interval 1.0–5.0 μg/dL [27.6–137.9 nmol/L]; cortisol post-administration of cosyntropin 21.1 μg/dL [582.1 nmol/L], reference interval 8.0–17.0 μg/dL [220.7–469 nmol/L]). Detectable levels of digoxin were measured using a competitive binding immunoassay, patient level 0.7 ng/mL (0.9 nmol/L), therapeutic reference interval 0.8–2.0 ng/mL (1–2.6 nmol/L). With no history of cardiac glycoside drug administration, this measured level was a result of oleander ingestion 24 h prior, confirming the diagnosis of oleander toxicosis.

Twenty-four hours after presentation, the arrhythmias had resolved, with the heart rate averaging 130 beats per minute and restoration of sinus rhythm seen on ECG. Appetite returned and nausea abated. However, recheck blood gas analysis (NOVA) revealed hypoglycemia (54 mg/dL [3 mmol/L], reference interval 75–116 mg/dL [4.2–6.4 mmol/L]). This result was verified with a portable handheld Alphatrak glucometer at 45 mg/dL (2.5 mmol/L). A bile acid test was performed, results of which were within normal limits (pre-feeding bile acids 1.2 μmol/L, reference interval <13 μmol/L; post-feeding sample 3.7 μmol/L, reference interval <25 μmol/L). The dog had eaten a meal consisting of around 1 oz (28 g) cooked chicken breast 6 h prior to the documented hypoglycemia and 0.5 oz (14 g) Hill's® j/d® canned food around 12 h prior. Due to the lack of clinical signs of hypoglycemia at this point, the dog was fed another 1 oz (28 g) cooked chicken breast and the blood glucose rechecked hourly. One hour later, hypoglycemia persisted at 72 mg/dL (4 mmol/L). A bolus of dextrose was administered (2 mL, 50 % dextrose diluted in 6 mL 0.9 % NaCl, IV). One hour following the bolus, the blood glucose was 147 mg/dL (8.2 mmol/L).

Six hours after the dextrose bolus, the dog appeared bright, alert, and responsive, with normal mentation. Euglycemia was restored, blood glucose 126 mg/dL (6.9 mmol/L). Due to the improved clinical signs, the dog was discharged.

Twenty-four hours after discharge, the dog was seen by the Internal Medicine Service for recheck evaluation. The only abnormal finding on physical examination was gelatinous skin turgor over the dorsum, thought to be remaining from prior subcutaneous drug administration. Other than this finding, the patient had made a full recovery, with normal heart rhythm, good appetite, and no vomiting.

## Discussion

This case report describes the first documented incidence of hypoglycemia associated with oleander toxicity. Often times in suspected poisoning cases, the etiologic agent cannot be documented. In this particular case, a positive result on the digoxin assay confirmed the witnessed ingestion. This test may be used to document oleander toxicosis, as there is cross reactivity between oleander and pure digoxin in the radioimmunoassay [8]. The levels measured on the digoxin

immunoassay are not necessarily correlated with the degree of clinical severity [3]. Blood oleandrin levels may correlate more closely with severity of toxicosis [3]; however, this test was unavailable. Also, high oleandrin levels have been documented in human patients with only mild clinical symptoms after oleander ingestion [3]. The assay was not repeated in this case, as its main purpose was documentation of ingestion. Further research would be needed to establish the pharmacokinetics of oleandrin and how this correlates to values obtained from the digoxin radioimmunoassay over time in dogs.

Classic clinical findings of oleander toxicosis were documented in this dog. In two separate canine studies [2, 9], intravenous oleander resulted in cardiac arrhythmias. Here, the severity of bradyarrhythmia was not enough to require treatment with atropine, and the degree of hyperkalemia was mild. It is unknown exactly why the dog collapsed at home. Hypovolemia is considered less likely as the dog received SC fluids. The collapse occurred after vomiting, so a vasovagal response is possible. A variety of factors, such as mild electrolyte imbalance, arrhythmia, and abdominal pain may have contributed.

This dog developed hypoglycemia presumed to be secondary to oleander toxicosis. In this dog, other possible causes of hypoglycemia were considered. Hypoadrenocorticism was ruled out with an ACTH stimulation test. Hepatic dysfunction was ruled out with a normal bile acid test. Sepsis was deemed highly unlikely due to lack of other criteria for sepsis and the clinical condition of the patient, who was asymptomatic at the time of hypoglycemia. There was no history of ingestion of any other known hypoglycemic agents or toxins such as xylitol. Small breed dogs can develop hypoglycemia after periods of anorexia. This dog was anorexic for approximately 48 h during the period of illness. However, it is considered unlikely that fasting produced the hypoglycemia in this dog, as the patient was in good body condition, ate several meals in the 12 h preceding the hypoglycemia, and remained hypoglycemic after eating. The most likely explanation was that the oleander had somehow resulted in hypoglycemia and lack of post-prandial hyperglycemia.

It is unknown why the dog was hypoglycemic after cardiac and gastrointestinal symptoms had resolved. There are no pharmacokinetic studies on oleander compounds and the effect on blood sugar in dogs, and no other case reports like this for comparison. It is thought that perhaps the oleander compounds had a delayed or prolonged effect on glucose metabolism in this particular dog.

Oleander is known to contain substances capable of reducing blood sugar levels [7]. Inhibition of alpha-glucosidase is thought to be one mechanism by which this effect occurs. Intestinal alpha-glucosidases in the small intestinal brush border hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose. Therefore, inhibition of this enzyme may result in hypoglycemia [10].

Theoretically, hypoglycemia could have resulted from inhibition of Na+K+ATPase resulting in decreased sodium gradient available for successful glucose transport.

The dog in this case was successfully managed symptomatically. Other therapies available in severe cases of canine oleander toxicosis include digoxin-specific Fab fragments [8] and Fructose-1,6-diphosphate [2]. Ideally, decontamination would have been performed by gastric lavage and activated charcoal administered. However, due to the timeframe between toxin ingestion and presentation to our hospital, this step was not performed. An enema could have been considered to help expel material from the colon.

In summary, this report describes the first documented case of hypoglycemia attributed to oleander toxicity in a dog. This finding is interesting as it supports the possible use of certain compounds found in Nerium oleander plants as potential therapeutic agents for blood glucose control.

**Conflict of Interest** No conflict of interest

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