ECG of the Month

A 2-year-old 30.5-kg (67.1-lb) neutered male Golden Retriever was presented for evaluation because of vomiting, anorexia, and severe lethargy. Two days prior to presentation, the dog ate the protective cover off an electric cable that was not connected to a power supply. The next day, the dog ate a lot of grass and vomited. Therefore, the owners isolated the dog in a vegetated area; that area contained several oleander plants (*Nerium oleander*). Subsequently, the dog vomited several more times. The owners discovered several oleander leaves in the vomited material.

On examination, the dog had tachycardia with a regular rhythm and a heart rate of 160 beats/min, respiratory rate of 32 breaths/min, and rectal temperature of 38.5°C (101.3°F). The dog was very weak and laterally recumbent. The mucous membranes were pink and slightly dry, and the capillary refill time was > 2 seconds. The pulse quality was weak. The rest of the physical examination findings were unremarkable. Oscillometric blood pressure measurement (systolic pressure, 107 mm Hg; diastolic pressure, 55 mm Hg) and an ECG examination were performed. A CBC revealed leukocytosis (27.8 X 10^9 WBCs/L; reference range, 6 X 10^9 to 12 X 10^9 WBCs/L), neutrophilia (24.2 X 10^9 neutrophils/L; reference range, 3 X 10^9 to 11.5 X 10^9 neutrophils/L), and a left shift (1.25 X 10^9 bands/L; reference range, 0 X 10^9 to 0.3 X 10^9 bands/L). Whole blood chemical analysis revealed that the dog was hypokalemic (3.2 mmol/L; reference range, 4.1 to 5.3 mmol/L) but normoglycemic. Ionized calcium and magnesium concentrations were not measured. Echocardiography revealed no abnormalities. On the basis of the dog's apparent oleander leaf ingestion and the clinical findings, a provisional diagnosis of oleander poisoning was made. The concentration of digoxinlike substances (oleandrin) in a serum sample was measured with a commercial digoxin assay[a] because oleandrin is known to cross-react with the anti-digoxin antibody, and the result was 0.69 nmol/L[1] (there should be no detectable amount of digoxinlike substances). Thus, the suspected diagnosis of oleander poisoning was confirmed. The serum concentration of cardiac troponin T[b] was 1.1 ng/mL (reference range, < 0.1 ng/mL).

This report was submitted by Robert Trujanovic, DVM; Alan Kovacevic, DVM; and Mark D. Kittleson, DVM, PhD; from the Clinical Unit of Anaesthesiology and Perioperative Intensive-Care Medicine, Vetmeduni Vienna, 1210 Vienna, Austria (Trujanovic); Section of Clinical Cardiology, Department of Clinical Small Animal Medicine, Vetsuisse Faculty, University of Bern, CH-3001 Bern, Switzerland (Kovacevic); and Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Kittleson).

Address correspondence to Dr. Trujanovic (trujanovicr@staff.vetmeduni.ac.at).

ECG Interpretation

The dog underwent an ECG examination, and tracings from leads I, II, and III were assessed **(Figure 1)**. The heart rate was 157 beats/min. No P waves were visible, compatible with the diagnosis of atrial standstill. Two distinct QRS-complex morphologies were present in an alternating pattern. One QRS-complex morphology (designated A) was positive, narrow, and of normal appearance in all 3 leads. There was borderline ST-segment depression of 0.15 to 0.2 mV in the type A QRS complexes. The other QRS-complex morphology (designated B) was also positive but wider with a large negative T wave in leads II and III. The A-A rhythm was regular and the A-B

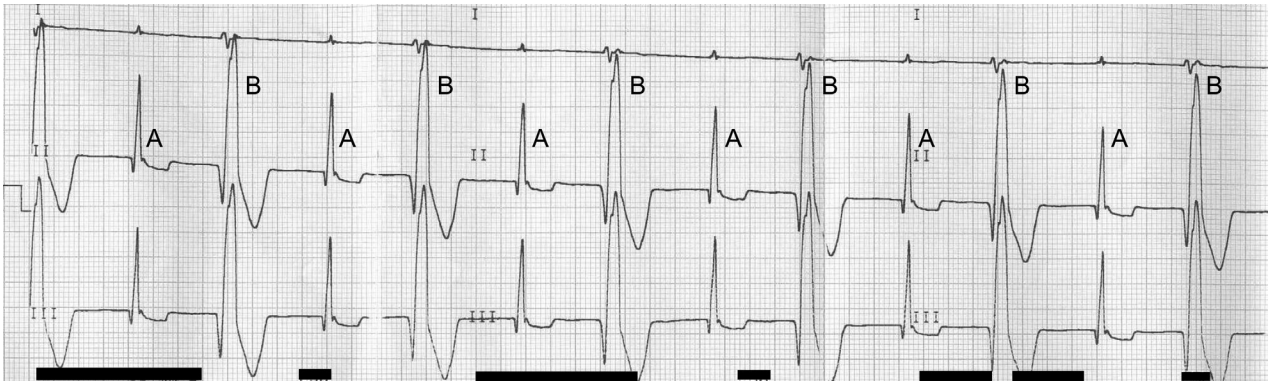

Figure 1—Lead I, II, and III tracings obtained from a 2-year-old dog that developed vomiting, anorexia, and severe lethargy after ingestion of oleander plants (*Nerium oleander*). The heart rate is 157 beats/min. No P waves are visible, which is compatible with atrial standstill. Two distinct QRS-complex morphologies alternate with one another. One type of QRS complex (A) is positive, normal, and narrow in all 3 leads; borderline ST-segment depression (0.15 to 0.2 mV) is present in these complexes. The other type of QRS complex (B) is also positive but wider with a large negative T wave in leads II and III. The rate of the normal complexes (A to A) was 75 complexes/min. The instantaneous rate of the large, bizarre-shaped QRS-T complexes (type B) was 143 complexes/min (420 milliseconds from A to B). Paper speed = 50 mm/s; 1 cm = 2 mV.

distance was fixed, but type B complexes appeared earlier than expected for type A complexes (ie, type B complexes were premature). The rate of the normal complexes (A to A) was 75 complexes/min. The instantaneous rate of the large bizarre-shaped QRS-T complexes (type B) was 143 complexes/min (420 milliseconds from A to B). Atrial standstill with a nodal escape rhythm and ventricular bigeminy in which the ventricular premature complexes (VPCs) did not alter that nodal escape rate (nodal entrance block) were diagnosed. Most nodal escape rhythms have a rate in the range of 40 to 65 beats/min,[2] so this nodal escape rhythm appeared slightly accelerated.

Discussion

Several cardiac glycosides are found in oleander plants (*N oleander*), including oleandrin and oleandrigenin.[3] These substances cause a reversible inhibition of the membrane Na^+,K^+-ATPase pump, which leads to an increased calcium concentration in the cardiac muscle cells. This increased calcium concentration leads to changes in the excitability (eg, delayed afterdepolarizations) and conduction properties of the cells.[4] As a result, various tachyarrhythmias can develop. Because VPCs are common with digitalis glycoside intoxication,[5] detection of VPCs in the ECG tracings obtained from the dog of the present report was not unexpected. Digitalis intoxication can also result in bradycardias, which are thought to be attributable to increased vagal tone caused by stimulation of the area postrema.[6] Administration of atropine is a treatment option for bradycardic arrhythmias in humans with digoxin intoxication.[7] We assumed that the main factor contributing to the weakness of the dog of the present report was the neurotoxic effect of oleandrin, which interferes with the fundamental processes that regulate the neuronal membrane potential. These findings have been described for other animals and > 80% of humans with oleander intoxication.[8,9]

Oleandrin is the most clinically relevant glycoside of the oleander plant. All plant parts contain glycosides, but the highest concentration is found in the red flowers.[10] The LD_{50} of oleandrin in dogs has not been reported, to our knowledge. In equids, consumption of dry oleander leaves at a dose of 0.005% of body weight is likely fatal.[11] Adam et al[12] claim that the oral uptake of 0.06 g of dried oleander leaves/kg of body weight in sheep is fatal.

Oleander poisoning in humans has been widely described.[1,13,14] In mammals, naturally occurring or experimentally induced oleander poisoning in horses,[15,16] a donkey,[11] a guinea pig,[17] cows,[18,19] cats,[20] monkeys,[21] sheep,[12] and rats[22] has been described. Many treatments for glycoside poisoning have been either used or recommended. Such treatments include those that specifically treat arrhythmias (eg, atropine, β-adrenoreceptor agonists, temporary pacing, magnesium, and phenytoin) and those that are intended to bind or neutralize glycosides (eg, multiple-dose–activated charcoal, fructose-1,6-diphosphate, anticalin, and anti-digoxin Fab antitoxin). Sodium bicarbonate could be used in a hyperkalemic patient to decrease serum potassium concentration.[23,24] There are reports that anti-digoxin Fab antitoxin may be an effective treatment for oleander poisoning in humans and dogs[23,25–27]; in dogs, fructose-1,6-diphosphate has been used for oleandrin toxicosis.[28]

The most common arrhythmias associated with cardiac glycoside toxicosis are sinus bradycardia, second-degree atrioventricular (AV) block, and VPCs.[2] Trautvetter et al[29] described AV block as a result of oleander intoxication in a dog. It is known that digoxin poisoning may induce atrial standstill in humans[7,30,31] and that atrial standstill is commonly accompanied by a junctional escape rhythm.[32] In a previous publication,[33] a Golden Retriever developed several types of arrhythmia during the course of oleander toxicosis that included ventricular tachycardia (monomorphic and polymorphic forms), accelerated idioventricular rhythm, VPCs, isorhythmic AV dissociation, second-degree AV block (Mobitz type I and II), and first-degree AV block. That dog was released for home care after 4 days of hospitalization; 4 days after discharge from the hospital, a clinical examination and ECG did not indicate any abnormalities and a sinus arrhythmia was detected.[33] To our knowledge, atrial standstill induced by oleander poisoning in a dog has not been previously described.

An increase in a biomarker of myocardial damage (creatine kinase myocardial band) has been reported for a donkey with oleander intoxication.[11] A more sensitive and specific indicator of myocardial damage in dogs is the circulating concentration of cardiac troponin T.[34] Notably high serum cardiac troponin T concentration was identified in the dog of the present report. We presumed that the glycoside toxicosis resulted in myocardial damage that led to myocardial cell death.

For the dog of the present report, the blood concentration of the digoxinlike substance was examined 4 times during an 8-day period, and values were 0.69 nmol/L on day 1 (the day of the initial evaluation), 0.4 nmol/L on day 4, 0.32 nmol/L on day 5, and 0.00 nmol/L on day 9. Hypokalemia was probably a result of vomiting and inappetence, and the dog was treated with an IV crystalloid infusion supplemented with potassium. Drugs to bind the glycosides were not used. The use of cholestyramine, a steroid binder of enterohepatic circulating digoxin,[35] was omitted because there are no data regarding the use of this binder in dogs with oleander poisoning and the general condition of the dog after initial treatment was stable. Atropine was not administered because the dog did not develop clinically relevant bradycardia. For cost reasons, the use of anti-digoxin antibodies was also omitted. Fructose-1,6-diphosphate was not available. A clinical examination and ECG of the dog several weeks it was discharged from the hospital did not reveal any abnormalities.

Footnotes

a. MEIA II assay for digoxin, AxSYM, Abbott Central Chemical Laboratory, Inselspital, Bern, Switzerland.
b. Cardiac reader, Roche, Roche Diagnostics AG, Rotkreuz, Switzerland.

References

1. Dasgupta A, Datta P. Rapid detection of oleander poisoning using digoxin immunoassays: comparison of five assays. *Ther Drug Monit* 2004;26:658–663.
2. Tilley LP. Analysis of common canine cardiac arrhythmias. In: Tilley LP, ed. *Essentials of canine and feline electrocardiography.* 2nd ed. Philadelphia: Lea & Febiger, 1992;127–207.
3. Jortani SA, Helm RA, Valdes R. Inhibition of Na,K-ATPase by oleandrin and oleandrigenin, and their detection by digoxin immunoassays. *Clin Chem* 1996;42:1654–1658.
4. Grace A. Cardiac arrhythmia. In: *Clinical pharmacology.* 11th ed. Philadelphia: Elsevier Inc, 2012;428–443.
5. Shapiro W. Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol* 1978;41:852–859.
6. Somberg JC. Digitalis: neurally mediated arrhythmogenic and coronary vasoconstrictor properties. *J Clin Pharmacol* 1985;25:529–539.
7. Smith TW, Willerson JT. Suicidal and accidental digoxin ingestion. Report of five cases with serum digoxin level correlations. *Circulation* 1971;44:29–36.
8. Rubini S, Rossi SS, Mestria S, et al. A probable fatal case of oleander (*Nerium oleander*) poisoning on a cattle farm: a new method of detection and quantification of the oleandrin toxin in rumen. *Toxins (Basel)* 2019;11:442.
9. Bandara V, Weinstein SA, White J, et al. A review of the natural history, toxinology, diagnosis and clinical management of *Nerium oleander* (common oleander) and *Thevetia peruviana* (yellow oleander) poisoning. *Toxicon* 2010;56:273–281.
10. Karawya MS, Balbaa SI, Khayyal SE. Estimation of cardenolides in *Nerium oleander. Planta Med* 1973;23:70–73.
11. Smith PA, Aldridge BM, Kittleson MD. Oleander toxicosis in a donkey. *J Vet Intern Med* 2003;17:111–114.
12. Ada SE, Al-Yahya MA, Al-Farhan AH. Acute toxicity of various oral doses of dried nerium oleander leaves in sheep. *Am J Chin Med* 2001;29:525–532.
13. Azzalini E, Bernini M, Vezzoli S, et al. A fatal case of self-poisoning through the ingestion of oleander leaves. *J Forensic Leg Med* 2019;65:133–136.
14. Wasfi IA, Zorob O, Al katheeri NA, et al. A fatal case of oleandrin poisoning. *Forensic Sci Int* 2008;179:e31–e36.
15. Chizzola R, Huber W, Siencnik I. Oleandervergiftung bei Pferden: Nachweis von Oleanderblättern im Mageninhalt - ein Fallbericht. *Wien Tierärztl Mschr* 1998;85:359.
16. Hughes KJ, Dart AJ, Hodgson DR. Suspected *Nerium oleander* (oleander) poisoning in a horse. *Aust Vet J* 2002;80:412–415.
17. Kirsch M. Acute glycoside intoxication from the intake of oleander (*Nerium oleander*) leaves in a guinea pig [in German]. *Tierarztl Prax Suppl* 1997;25:398–400.
18. Galey FD, Holstege DM, Plumlee KH, et al. Diagnosis of oleander poisoning in livestock. *J Vet Diagn Invest* 1996;8:358–364.
19. Oryan A, Maham M, Rezakhani A, et al. Morphological studies on experimental oleander poisoning in cattle. *Zentralbl Veterinarmed A* 1996;43:625–634.
20. Meyer HP, van der Linden WJ, van der Linde-Sipman JS. A case of oleander poisoning in a cat [in Dutch]. *Tijdschr Diergeneeskd* 1993;118:436–438.
21. Schwartz WL, Bay WW, Dollahite JW, et al. Toxicity of *Nerium oleander* in the monkey (*Cebus apella*). *Vet Pathol* 1974;11:259–277.
22. Pahwa R, Chatterjee VC. The toxicity of yellow oleander (*Thevetia neriifolia juss*) seed kernels to rats. *Vet Hum Toxicol* 1990;32:561–564.
23. Roberts DM, Buckley NA. Antidotes for acute cardenolide (cardiac glycoside) poisoning. *Cochrane Database Syst Rev* 2006;CD005490.
24. Roberts DM, Gallapatthy G, Dunuwille A, et al. Pharmacological treatment of cardiac glycoside poisoning. *Br J Clin Pharmacol* 2016;81:488–495.
25. Clark RF, Selden BS, Curry SC. Digoxin-specific Fab fragments in the treatment of oleander toxicity in a canine model. *Ann Emerg Med* 1991;20:1073–1077.
26. Eddleston M, Senarathna L, Mohamed F, et al. Deaths due to absence of an affordable antitoxin for plant poisoning. *Lancet* 2003;362:1041–1044.
27. Pao-Franco A, Hammond TN, Weatherton LK, et al. Successful use of digoxin-specific immune Fab in the treatment of severe *Nerium oleander* toxicosis in a dog. *J Vet Emerg Crit Care (San Antonio)* 2017;27:596–604.
28. Markov AK, Payment MF, Hume AS, et al. Fructose-1,6-diphosphate in the treatment of oleander toxicity in dogs. *Vet Hum Toxicol* 1999;41:9–15.
29. Trautvetter E, Kasbohm C, Werner J. Oleander poisoning with respiratory AV block in a dog [in German]. *Berl Munch Tierarztl Wochenschr* 1969;82:306–308.
30. Citrin DL, O'Malley K, Hillis WS. Cardiac standstill due to digoxin poisoning successfully treated with atrial pacing. *Br Med J* 1973;2:526–527.
31. Bernstein MS, Neschis M, Collini F. Treatment of acute massive digitalis poisoning by administration of a chelating agent. *N Engl J Med* 1959;261:961–962.
32. Vallé B, Lairez O, Gandia P, et al. Circuitous diagnosis in concealed self-poisoning with *Nerium oleander. Clin Toxicol (Phila)* 2012;50:228–229.
33. Kovacevic A, Gerold A, Lombard CW. Oleander poisoning in a Golden Retriever [in German]. *Kleintierpraxis* 2004;49:441–446.
34. O'Brien PJ, Dameron GW, Beck ML, et al. Differential reactivity of cardiac and skeletal muscle from various species in two generations of cardiac troponin-T immunoassays. *Res Vet Sci* 1998;65:135–137.
35. Roberge RJ, Sorensen T. Congestive heart failure and toxic digoxin levels: role of cholestyramine. *Vet Hum Toxicol* 2000;42:172–173.