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Anesthesia Case of the Month

History

A 4-year-old 800-g (1.8-lb) spayed female ferret (*Mustela putorius furo*) was brought to the University of Georgia Veterinary Teaching Hospital for evaluation of an enlarged vulva of several weeks' duration. Laboratory testing revealed high plasma estradiol (471 pmol/L; reference range,[1] 30 to 108 pmol/L) and 17-hydroxyprogesterone (2.6 nmol/L; reference range,[1] < 0.1 to 0.8 nmol/L) concentrations, consistent with adrenocortical disease. Treatment was declined by the owner at this time on financial grounds; however, the ferret was readmitted 3 months later for adrenalectomy.

Results of preoperative hematologic and serum biochemical testing were unremarkable. In preparation for surgery, abdominal ultrasonography was performed to determine which adrenal gland was affected. An isoechoic to slightly hyperechoic nodule was seen in the cranial pole of the left adrenal gland, which was also enlarged, compared with the right adrenal gland. There was no evidence of caudal vena cava invasion. The ferret appeared bright and alert on the morning of the scheduled surgery. The only abnormal physical examination finding was vulvar swelling.

The ferret was premedicated with butorphanol (0.2 mg/kg [0.09 mg/lb], IM) and midazolam (0.5 mg/kg [0.23 mg/lb], IM). Within a few minutes, the ferret became quite sedate and lost the righting reflex. Supplemental oxygen was provided by mask, and a Doppler ultrasonic flow detector[a] was placed on one of the forelimbs with a size 1 cuff applied proximally on the limb for measurement of systolic blood pressure. A 24-gauge IV catheter was placed in a cephalic vein, and the ferret was prepared for surgery.

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During preparation of the ferret for surgery, an irregular pulse rate was heard with the Doppler ultrasonic flow detector, and electrocardiography was performed to assess heart rate and rhythm. Systolic blood pressure was estimated to be 130 mm Hg at this time. Examination of the ECG revealed an irregularly irregular supraventricular rhythm (QRS duration, 0.02 seconds; reference range,[2] 0.035 to 0.06 seconds) with a QRS rate of 190 beats/min and an absence of P waves (**Figure 1**). There appeared to be fine baseline undulation consistent with fibrillation waves. Motion artifact was considered unlikely, given that the patient was sedated. On the basis of the ECG findings, a diagnosis of atrial fibrillation was made.

Question

What is the most likely cause of the arrhythmia in this ferret?

Answer

Increased vagal tone induced by butorphanol[3] was suspected to be the cause of the atrial fibrillation in this patient. Atrial fibrillation is a common arrhythmia that can present as an isolated problem but is often associated with structural heart disease. The condition has been described in several species, including humans, dogs (most often large- and giant-breed dogs), and horses.[4–6] Large atrial size and increased vagal tone are 2 predisposing factors for this rhythm disturbance in horses and giant-breed dogs with cardiomyopathy.[5,6] Atrial fibrillation can develop in ferrets with substantial atrial enlargement but is not considered to be a common arrhythmia in this species.[2] Differential diagnoses for atrial fibrillation include atrial enlargement secondary to underlying cardiovascular disease, large atrial size without structural disease (eg, in giant-breed dogs and horses), altered autonomic tone, and irritation of the atrial myocardium (eg, blunt trauma and central venous catheter placement).

After atrial fibrillation was identified in the ferret, surgery was postponed to allow investigation of the un-

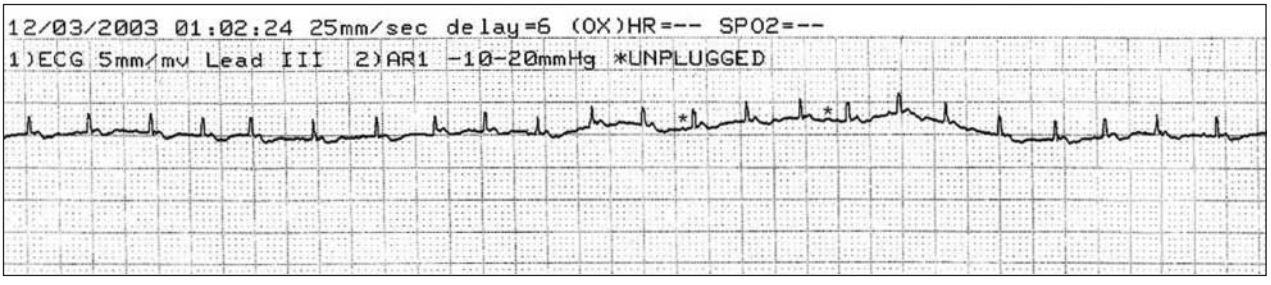

Figure 1—Lead III ECG of a ferret sedated with butorphanol and midazolam. Notice the irregular R-R interval, absence of P waves, and fine baseline undulation consistent with fibrillation waves (asterisks). Paper speed = 25 mm/s; 1 cm = 2 mV.

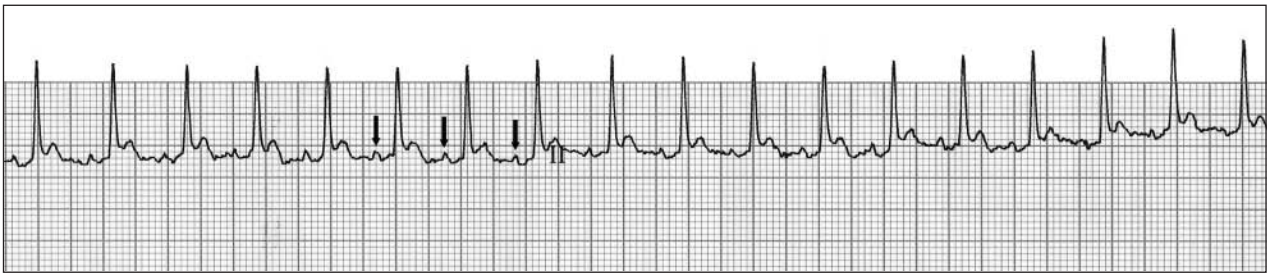

Figure 2—Lead II ECG obtained 5 hours later from the ferret in Figure 1. Notice the regular R-R interval and P waves (arrows). Paper speed = 25 mm/s; 1 cm = 2 mV.

derlying cause. The ferret was allowed to recover from the effects of premedication in an oxygen cage, and fluids were administered IV. Systolic blood pressure was not measured during this time owing to difficulties in handling the patient without sedation. The patient appeared to have completely recovered from the effects of premedication 2 hours later. Follow-up electrocardiography was performed 5 hours after butorphanol and midazolam had been given and revealed a normal sinus rhythm (**Figure 2**). Echocardiography was not performed because of financial constraints.

When checking the anesthetic plan for this patient, it was discovered that there had been a miscalculation of the butorphanol dose. Instead of the intended dose of 0.2 mg/kg, the ferret had been administered a dose that was 10 times as high (2 mg/kg [0.9 mg/lb]). A reversal agent was not given because the error was not discovered until after the ferret had recovered from the sedative effects.

The ferret was rescheduled for surgery 48 hours after the first attempt. The patient was premedicated with hydromorphone (0.1 mg/kg [0.045 mg/lb], IM) and glycopyrrolate (0.01 mg/kg [0.0045 mg/lb], IM), and 25 minutes later, anesthesia was induced with isoflurane (4%) administered by mask. A 3-mm-diameter endotracheal tube was inserted, and anesthesia was maintained with isoflurane in oxygen. A Doppler ultrasonic flow detector was placed on one of the forelimbs, and the patient was prepared for surgery. No arrhythmias were identified before or during surgery. Systolic blood pressure, measured indirectly 15 and 20 minutes after induction, was estimated to be 100 and 90 mm Hg, respectively. Additional measurements of systolic blood pressure were not obtained during surgery because of technical difficulties. Following surgery, the ferret recovered from anesthesia without complications.

Discussion

Atrial fibrillation can be easily detected by means of electrocardiography and is characterized by irregularly irregular R-R intervals with replacement of the P waves by random fine baseline undulations.[6] It is important to differentiate between atrial fibrillation and baseline noise associated with skeletal muscle fasciculation. In the ferret described in the present report, the R-R interval was irregularly irregular, whereas with muscle fasciculation, the R-R interval is typically regular. Also, the ferret was deeply sedated and no abnormal skeletal muscle activity was observed.

Drugs that increase or decrease adrenergic or vagal tone may cause atrial fibrillation.[4] Mechanisms of drug-induced atrial fibrillation that have been described in people include adrenergic and vagal stimulation; direct cardiotoxicosis; changes in atrial conduction, refractoriness, or automaticity; coronary vasoconstriction or ischemia; and local electrolyte disturbances. In dogs, atrial fibrillation has been induced with fentanyl and pentobarbital,[7] and vagomimetic drugs have been shown to be associated with spontaneous atrial fibrillation in large-breed dogs.[8] These findings support the suggestion that vagal tone is an important contributor to the development of atrial fibrillation.

Opioids in general have excellent analgesic properties and a wide margin of safety.[9] Potent μ-opioid receptor agonists such as morphine and oxymorphone can cause ileus and sedation in small mammals, whereas mixed opioid receptor agonist-antagonists such as buprenorphine and butorphanol typically are associated with fewer adverse effects and are more commonly used.[b] The effects of opioids on the cardiovascular system are variable, depending on the species. In ferrets and rats, opioids tend to induce hypotension, whereas in rabbits and mice, they may cause hypertension.[9] Butorphanol continues to be the most commonly used opioid in ferrets despite recent questions regarding its analgesic properties.[9] Described as an opioid receptor agonist-antagonist, its agonist activity is exerted at κ-opioid receptors and its antagonist actions are exerted at μ-opioid receptors. Drugs in this class exert a ceiling effect, after which higher doses do not produce any further analgesia.[9,b]

Several studies[10,11] have evaluated the sedative and cardiorespiratory effects of various tranquilizer combinations that included butorphanol. None of these studies reported development of arrhythmias; however, the doses used were a tenth to a twentieth of the dose administered to the ferret in the present report (ie, 0.1 to 0.2 mg/kg).

Evidence associating drugs with atrial fibrillation is scant and largely based on individual case reports. Usually, it is not difficult to diagnose drug-induced atrial fibrillation because there is a direct temporal relationship between administration of the drug and the onset of atrial fibrillation.[4] In the ferret described in the present report, the overdose of butorphanol was considered to be the most likely cause of the atrial fibrillation. Because echocardiography was not performed, cardiac disease could not be ruled out. However, the ferret appeared overtly healthy and did not

have any clinical signs associated with cardiac disease (eg, lethargy, exercise intolerance, weight loss, anorexia, ascites, coughing, dyspnea, or hind limb weakness).[2] In addition, even though butorphanol is commonly used for premedication and analgesia in small mammals, it is considered to have an especially profound sedative effect in this species,[b] supporting the theory that increased vagal tone was the trigger for the atrial fibrillation that was observed. The arrhythmia resolved once the effects of butorphanol were gone, and sedation with an appropriate dose of a μ-opioid receptor agonist 2 days later did not induce any rhythm disturbances.

The ferret described in the present report did have an underlying disease that may have predisposed it to develop atrial fibrillation. In people, glucocorticoid use is associated with a 2-fold risk of atrial fibrillation,[12] so it is possible that high plasma hormone concentrations in this ferret were a predisposing factor. A combination of primary aldosteronism and atrial fibrillation has been reported in 5 human patients with hypersecretion of aldosterone secondary to an adenoma,[13] and another case report[14] described a domestic ferret with primary aldosteronism secondary to an aldosterone-producing adrenal gland neoplasm. Plasma aldosterone and potassium concentrations were not measured in the ferret described in the present report but likely were abnormal, given the abnormal plasma estradiol and 17-hydroxyprogesterone concentrations.

Because of their small size, it is important to have accurate measurements of body weight when calculating drug dosages for small mammals and to reweigh animals to detect any changes in body weight during hospitalization. Some drugs may have to be diluted to have an adequate volume for precise dosing in these small pets, but care should be taken to label diluted drugs to prevent mistakes in administration.

If an anesthetic drug overdose does occur, the most important initial step is to antagonize the drug's effects on the cardiovascular and respiratory systems with a reversal agent, if available. An opioid receptor antagonist can be used to reverse most effects associated with high-dose opioid administration, including respiratory depression and bradycardia.[c] However, these should be used cautiously in animals that have preexisting cardiac abnormalities and in animals that have received high doses of narcotics. In the present case, an opioid receptor antagonist was not administered because by the time the overdose was discovered, the ferret's condition was stable and no adverse effects associated with opioid administration were seen.

Appropriate supportive care should be administered to animals given an anesthetic drug overdose. This may include oxygen administration and fluid therapy along with specific treatment of any adverse effects that develop, including adverse CNS effects, cardiovascular abnormalities, and respiratory depression.[d] If arrhythmias develop, antiarrhythmic treatment should be considered after identification of the abnormal rhythm. An irregular rhythm can have a negative effect on hemodynamic stability; therefore, IV administration of fluids should be considered to maintain circulating blood volume, blood pressure, and cardiac output.

In conclusion, even though opioids have a wide margin of safety and can be used effectively for sedation and analgesia in ferrets, because most adverse drug reactions are dose related,[d] careful attention should be paid to dosing. Even when administered at recommended doses, opioids may cause profound sedation in some ferrets. Thus, ferrets should always be monitored closely when given these drugs. Arrhythmias that develop during an anesthetic episode should always be investigated, and if a drug is suspected as the underlying cause, administration of the drug should be discontinued and an antagonist given if available. After stabilization of the patient's condition, more-thorough evaluation of the cardiovascular system may be pursued.

a. Model 811-B, Parks Medical Electronics, Aloha, Ore.
b. Carpenter J. Pharmacotherapeutics in exotic small mammals: an update and review (abstr), in *Proceedings*. 31st Cong World Small Anim Vet Assoc 2006.
c. Fordham M. Analgesia and anesthesia for small mammals (abstr), in *Proceedings*. 13th Int Vet Emerg Crit Care Symp 2007.
d. Dowling P. Adverse drug reactions: recognition and management (abstr), in *Proceedings*. 76th West Vet Conf 2004.

References

1. Quesenberry KE, Rosenthal KL. Endocrine disorders. In: Quesenberry KE, Carpenter JW, eds. *Ferrets, rabbits and rodents: clinical medicine and surgery*. 2nd ed. St Louis: Saunders, 2005; 79–90.
2. Petrie JP, Morrisey JK. Cardiovascular and other diseases. In: Quesenberry KE, Carpenter JW, eds. *Ferrets, rabbits and rodents: clinical medicine and surgery*. 2nd ed. St Louis: Saunders, 2005;58–71.
3. Kushner LI, Calvert CA. Perianesthetic arrhythmias. *Compend Contin Educ Pract Vet* 2000;22:61–73.
4. van der Hooft CS, van Herpen G, Kors JA, et al. Drug-induced atrial fibrillation. *J Am Coll Cardiol* 2004;44:2117–2124.
5. Westling J, Westling W, Pyle RL. Epidemiology of atrial fibrillation in the dog. *Intern J Appl Res Vet Med* 2008;6:151–154.
6. Marr CM. Update on atrial fibrillation, in *Proceedings*. 10th Int Cong World Equine Vet Assoc 2008;127–130.
7. Pariaut R, Moise S, Koetje BD, et al. Evaluation of atrial fibrillation induced during anesthesia with fentanyl and pentobarbital in German Shepherd Dogs with inherited arrhythmias. *Am J Vet Res* 2008;69:1434–1445.
8. Moise NS, Pariaut R, Gelzer ARM, et al. Cardioversion with lidocaine of vagally associated atrial fibrillation in two dogs. *J Vet Cardiol* 2005;7:143–148.
9. Lichtenberger M. Anesthesia and analgesia for small mammals and birds. *Vet Clin North Am Exot Anim Pract* 2007;10:293–315.
10. Ko JC, Villareal A, Kuo WC, et al. Evaluation of sedative and cardiorespiratory effects of diazepam-butorphanol, acepromazine-butorphanol, and xylazine-butorphanol in ferrets. *J Am Anim Hosp Assoc* 1998;34:242–250.
11. Ko JC, Heaton-Jones TG, Nicklin CF. Evaluation of the sedative and cardiorespiratory effects of medetomidine, medetomidine-butorphanol, medetomidine-ketamine, and medetomidine-butorphanol-ketamine in ferrets. *J Am Anim Hosp Assoc* 1997;33:438–448.
12. Christiansen CF, Christensen S, Mehnert F, et al. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. *Acta Intern Med* 2009;169:1677–1683.
13. Watson T, Karthikeyan VJ, Lip GY, et al. Atrial fibrillation in primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 2009;10:190–194.
14. Desmarchelier M, Lair S, Dunn M, et al. Primary hyperaldosteronism in a domestic ferret with an adrenocortical adenoma. *J Am Vet Med Assoc* 2008;233:1297–1301.