Successful management of minoxidil toxicosis in a dog

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CASE DESCRIPTION

A 2-year-old sexually intact female mixed-breed dog was evaluated at an emergency hospital approximately 5 hours after ingestion of an unknown amount of over-the-counter topical hair growth promoter containing 5% minoxidil foam. Vomiting and signs of lethargy were reported by the owner, and physical examination revealed tachycardia and hypotension. No treatments were performed, and the dog was transferred to a veterinary referral hospital for management of suspected minoxidil toxicosis.

CLINICAL FINDINGS

On arrival at the referral hospital, the dog was tachycardic (heart rate, 200 to 220 beats/min) and hypotensive (systolic arterial blood pressure, 70 mm Hg). Electrocardiography revealed a regular, narrow-complex tachycardia with no evidence of ventricular ectopy.

TREATMENT AND OUTCOME

Hypotension was effectively managed with a constant rate infusion of dopamine hydrochloride (12.5 µg/kg/min [5.7 µg/lb/min], IV). Once normotensive, the dog remained tachycardic and a constant rate infusion of esmolol hydrochloride (40 µg/kg/min [18.2 µg/lb/min], IV) was initiated for heart rate control. A lipid emulsion was administered IV as a potential antidote for the toxic effects of the lipophilic minoxidil, with an initial bolus of 1.5 mL/kg (0.7 mL/lb) given over 15 minutes followed by a continuous rate infusion at 0.25 mL/kg/min (0.11 mL/lb/min) for 60 minutes. While hospitalized, the dog also received maropitant citrate and ondansetron. Resolution of clinical signs was achieved with treatment, and the dog was discharged from the hospital 36 hours after admission. Four days later, the owner reported that the dog had made a full recovery and had returned to its typical behavior and activity level at home.

CLINICAL RELEVANCE

To the authors’ knowledge, this is the first report of successful clinical management of accidental minoxidil toxicosis in a dog. (J Am Vet Med Assoc 2018;252:222–226)

ABBREVIATIONS

bpm Beats per minute
CRI Continuous rate infusion
IVLE Lipid emulsion for IV administration
SAP Systolic arterial blood pressure

A 2-year-old 5.8-kg (12.8-lb) sexually intact female mixed-breed dog was brought to an emergency hospital because of vomiting and signs of lethargy observed after the dog had licked the scalp of a person recently self-treated with a topical 5% minoxidil foam. The exact amount ingested was unknown. Approximately 30 minutes after exposure, the dog appeared lethargic and vomited twice. Signs of lethargy continued throughout the evening, and the owner suspected tachycardia from observing the dog’s precordial impulses, prompting the emergency visit.

On arrival at the emergency hospital approximately 5 hours after minoxidil exposure, the dog appeared lethargic, with a rectal temperature of 37.5°C (99.5°F; reference interval, 37.5° to 39.2°C [99.5° to 102.5°F]) and a respiratory rate of 30 breaths/min (reference interval, 10 to 35 breaths/min). Electrocardiography revealed a regular, narrow-complex tachycardia with a heart rate of 233 bpm (reference interval, 70 to 140 bpm). The dog was hypotensive, with a Doppler-derived SAP of 62 mm Hg (reference interval, 90 to 140 mm Hg). No treatments were performed, and the dog was transferred to a veterinary referral hospital for management of suspected minoxidil toxicosis.

On admission to the referral hospital that same day, the dog was quiet, alert, and responsive, with an unremarkable rectal temperature (38.6°C [101.1°F]) and respiratory rate (16 breaths/min) and markedly high heart rate (210 bpm). The dog was eucneic, had strong and synchronous femoral pulses with no pulse deficits, and had tacky mucous membranes. Other physical examination findings were unremarkable. Electrocardiography was performed, revealing a regular, narrow-complex tachycardia with a heart rate of 200 to 220 bpm and no evidence of ventricular ectopy. The dog was also hypotensive, with a Doppler-derived SAP of 70 mm Hg. A 20-gauge peripheral catheter was placed in the right cephalic vein, and blood samples were collected during catheter placement for clinicopathologic testing. These tests
revealed hemoconcentration with a PCV of 50% (reference interval, 35% to 45%) and a plasma total protein concentration of 8 g/dL (reference interval, 6.5 to 8.0 g/dL), mild hyperlactatemia (blood lactate concentration, 3.0 mmol/L; reference interval, 0.5 to 2.5 mmol/L), mild azotemia (blood creatinine concentration, 1.7 mg/dL; reference interval, 0.6 to 1.6 mg/dL); BUN concentration, 28 mg/dL (reference interval, 5 to 20 mg/dL), mild hyponatremia (blood sodium concentration, 139.1 mmol/L; reference interval, 143 to 150 mmol/L), mild hypokalemia (blood potassium concentration, 3.18 mmol/L; reference interval, 3.5 to 4.8 mmol/L), mild hypochloremia (blood sodium concentration, 108.7 mmol/L; reference interval, 111 to 119 mmol/L), and mild hyperglycemia (blood glucose concentration, 183 mg/dL; reference interval, 78 to 126 mg/dL).

Fluid resuscitation was initiated with a 100-mL bolus of isotonic crystalloid fluid5 (17 mL/kg [7.7 mL/lb]) administered IV over a 15-minute period. Afterward, the dog remained hypotensive with an SAP of 80 mm Hg. No additional fluids were given.

The dog was transferred to the intensive care unit for continued care. Continuous telemetry monitoring was initiated at this time. Hypotension was managed with a CRI of dopamine hydrochloride,6 starting at a rate of 5 µg/kg/min (2.3 µg/lb/min), IV. This rate was increased in increments of 2.5 µg/kg/min (1.1 µg/lb/min) by titrating to effect on the basis of serial SAP measurements until a rate of 12.5 µg/kg/min (5.7 µg/lb/min) was reached. An additional 20-gauge catheter was placed in the left cephalic vein, and a dose of IVL6 was given, starting with an initial bolus of 1.5 mL/kg (0.7 mL/lb) administered over a 15-minute period, followed by a CRI of 0.25 mL/kg/min (0.11 mL/lb/min) for 60 minutes. Blood pressure then normalized to an SAP of 110 mm Hg. By 6 hours after transfer to the intensive care unit, blood lactate concentration had also normalized (1.5 mmol/L).

Despite blood pressure normalization, the dog remained tachycardic, with a heart rate ranging from 197 to 217 bpm. Electrocardiography revealed continued regular, narrow-complex tachycardia with no evidence of ventricular ectopy. Subsequently, β-blocker treatment was initiated for heart rate control. Five boluses of esmolol hydrochloride7 (each at 50 µg/kg [22.7 µg/lb]) were administered IV at 15-minute intervals until a heart rate < 200 bpm was attained. Then an esmolol CRI was initiated at a rate of 10 µg/kg/min (4.5 µg/lb/min), IV. The infusion was titrated to effect to a maximum rate of 60 µg/kg/min (27 µg/lb/min) and subsequently decreased to 40 µg/kg/min (18 µg/lb/min) because the dog had mild hypotension (SAP, 80 mm Hg) at the higher rate.

Heart rate gradually decreased and stabilized to between 100 to 145 bpm with a normal sinus rhythm approximately 6 hours after the esmolol CRI began. Systolic arterial blood pressure stabilized at 110 mm Hg once the rate of the esmolol CRI was adjusted to 40 µg/kg/min. The dog vomited twice 15 hours after hospital admission and was given a single dose of ondansetron8 (0.2 mg/kg [0.09 mg/lb], IV). The dog vomited twice approximately 8 hours after receiving ondansetron and was given a single dose of maropitant citrate9 (1 mg/kg [0.45 mg/lb], IV). Afterward, no additional episodes of vomiting occurred. The esmolol CRI was discontinued after 12 hours because of extravasation of the IV catheter, and the dog's heart rate remained stable between 125 and 180 bpm without β-blocker treatment.

Because of the owner's financial constraints, the dog was discharged from the hospital approximately 36 hours after admission against medical advice. The dopamine CRI was discontinued, and the dog's heart rate and SAP at that point were 172 bpm and 80 mm Hg, respectively. Four days later, the owner contacted the Emergency and Critical Care Service at the referral hospital and reported that the dog had made a full recovery and had returned to its typical behavior and activity level at home.

**Discussion**

Minoxidil is an ATP-sensitive potassium channel opener with potent vasodilatory effects.1-3 The drug produces systemic hypotension by directly relaxing the arteriolar smooth muscle. Minoxidil was originally marketed and prescribed in human medicine for the treatment of refractory hypertension; however, after hypertrichosis was noted to be a common adverse effect, minoxidil became widely commercially available in a 2% and 5% over-the-counter topical treatment for male and female androgenic alopecia.2,5 Minoxidil has also been proposed as a treatment for alopecia in dogs, but because of the severe cardiovascular toxic effects observed in both cats and dogs, the use of oral or topical preparations is not currently recommended for veterinary species.5,6

Minoxidil is rapidly absorbed from the gastrointestinal tract, producing peak plasma concentrations within 1 hour after administration in humans2 and within 2 hours after administration in dogs.1 The drug is primarily metabolized by the liver, non–protein bound, and exclusively excreted by glomerular filtration.2 Plasma concentrations of minoxidil poorly correlate with its antihypertensive effects. Despite a half-life of approximately 4 hours,2,4 the duration of action of a single dose may be > 72 hours in humans2 and at least 24 hours in dogs.1 The exact duration of action of a single dose of minoxidil in dogs is unknown.

Clinical signs of minoxidil toxicosis in dogs have been well characterized through experimental research and include exaggerated carotid pulsation, tachycardia, and hypotension.1 Secondary to the profound hemodynamic effects of the drug, cardiovascular lesions are reported to occur in dogs with short-term oral administration at a dose of 0.5 to 2 mg/kg (0.2 to 0.9 mg/lb) and include left ventricular subendocardial and papillary necrosis, right atrial hemorrhage, and coronary arteritis.1,7,8
Reports of suspected minoxidil toxicosis in cats consist of a single retrospective case series in which the clinical signs and course of a 3-year-old and 7-year-old castrated male domestic shorthair cat were described. Both cats were initially evaluated for signs of anorexia, lethargy, and dyspnea approximately 36 and 72 hours following topical application of a minoxidil solution to focal areas of alopecia. Both cats were found to have evidence of cardiac dysfunction, pulmonary edema, myocardial interstitial edema, myodegeneration, myocarditis, and acute myocardial ischemia. Specific treatments were not reported, and further cardiovascular diagnostics not pursued; however, the authors of that report advocated aggressive cardiovascular and respiratory monitoring to screen for evidence of cardiac dysfunction, pulmonary edema, and pleural effusion in cats with known minoxidil exposure.

Although the mechanisms underlying the hemodynamic and cardiotoxic effects of minoxidil have been thoroughly described for dogs, no management options for minoxidil toxicosis have been reported for this species. To the authors' knowledge, the present report represents the first of successful management of a veterinary patient with toxicosis following ingestion of an over-the-counter topical hair growth promoter containing 5% minoxidil foam.

The dog of the present report developed signs consistent with minoxidil toxicosis approximately 5 hours after exposure. Given that minoxidil reportedly reaches peak plasma concentrations in dogs within 2 hours after administration, no emesis was induced because such action was considered unlikely to change the clinical outcome. In human medicine, activated charcoal has been administered in some cases of minoxidil overdose to provide gastrointestinal decontamination. Owing to the rapid absorption of minoxidil from the gastrointestinal tract, time from ingestion to initial veterinary evaluation, and route of excretion, activated charcoal was not administered to the dog of the present report because such action was also considered unlikely to change clinical outcome.

Management of minoxidil overdose in humans primarily involves supportive care, consisting of blood pressure support through careful IV administration of fluids and administration of peripherally acting α-adrenoceptor agonists. Dopamine and phenylephrine, both strong α1-adrenoceptor agonists, are the vasopressors of choice to mitigate antihypertensive effects in humans with minoxidil overdose. Dopamine stimulates β1 adrenoceptors, increasing heart rate and contractility, at intermediate infusion rates (3 to 10 μg/kg/min [1.4 to 4.5 μg/lb/min]) and predominantly produces α1-adrenoceptor-mediated vasoconstriction at higher rates (10 to 20 μg/kg/min [4.5 to 9.1 μg/lb/min]). However, considerable variation and overlap in effects can exist among individuals, and published dose ranges should be considered guidelines only. For this reason, an initial infusion dopamine dose of 5 μg/kg/min was titrated to effect for the dog of the present report to a final infusion dose of 12.5 μg/kg/min, which resulted in resolution of hypertension.

Dopamine was selected over phenylephrine owing to drug availability and cost considerations. General recommendations are to avoid medications with strong β-adrenergic effects, including epinephrine and norepinephrine (which has modest β-adrenergic activity), in patients with minoxidil toxicosis because such medications may increase chronotropy and inotropy, exacerbating myocardial oxygen demand and precipitating myocardial ischemia. In a case report of human minoxidil toxicosis, midodrine, which is a selective α1-adrenoceptor agonist for oral administration, was prescribed and successfully used to manage hypotension. Midodrine may serve as an additional treatment option, providing blood pressure support without the need for intensive care.

The dog of the present report remained tachycardic despite being normotensive, prompting the use of esmolol for heart rate control. Esmolol is an ultrashort-acting β1-adrenoceptor blocker that provides negative chronotropic and inotropic activity by inhibiting adrenergic stimulation of β1-adrenoceptors within the sinoatrial node and myocardium. The drug also slows atrioventricular nodal conduction. Esmolol has a terminal half-life of 10 minutes and was selected because it could be easily titrated to effect and adjusted if secondary hypotension was encountered. The drug has been prescribed in veterinary medicine as a trial treatment to determine whether β-blocker administration would be effective against a particular arrhythmia as well as in a CRI for the short-term management of supraventricular arrhythmias, including atrial fibrillation, flutter, and sinus tachycardia. The dog of the present report was considered to be at risk of myocardial ischemia, so esmolol was administered in an attempt to further decrease myocardial oxygen demand and increase myocardial perfusion.

Diltiazem could also have been considered to manage the tachycardia. Diltiazem is a calcium channel blocker that decreases the ventricular response rate by prolonging atrioventricular nodal conduction and its respective refractory period. However, diltiazem is generally contraindicated in patients with severe hypotension (< 90 mm Hg) and acute myocardial infarction, which were both concerns for the dog of the present report. The choice of esmolol over diltiazem was based on clinician preference and discretion.

The regular, narrow-complex tachycardia in the dog of the present report was interpreted as a supraventricular tachycardia. This pattern is defined as rapid heart rhythms, typically exceeding 180 to 200 bpm in dogs, that originate or involve at least 1 cardiac structure above the ventricles, including the...
atra or atrioventricular junction.17 Differential mechanisms for the suspected supraventricular tachycardia included focal atrial tachycardia, atrial flutter, and orthodromic atrioventricular reentrant tachycardia.17 It is important to note that this rhythm could not be definitively differentiated from reflex sinus tachycardia in the dog. However, reflex sinus tachycardia was deemed less likely given that the regular, narrow-complex tachycardia persisted once the dog became normotensive. Persistence of tachycardia despite achievement of normotension has also been reported for 2 humans with minoxidil overdose and has been associated with markedly high cardiac output associated with low systemic vascular resistance.5,9,10 To the authors’ knowledge, supraventricular tachycardia has not been previously described as a clinical finding in veterinary species with minoxidil toxicosis. Although the limitations imposed on case management made it impossible to identify the cause of the suspected supraventricular tachycardia and its underlying mechanism in the dog of the present report, myocardial hypoxia and ischemia could have been involved.

The use of IVLE has gained popularity in veterinary emergency medicine as a promising antidote for toxicoses caused by various highly lipophilic drugs.18 This use has been proposed to exert an effect by improving cardiac function or acting as a so-called lipid sink, whereby fat-soluble toxic agents are sequestered into a newly formed lipid compartment within the intravascular space and then eliminated.18 The usefulness of IVLE in veterinary medicine varies and depends on the fat solubility of the given drug, with the effectiveness of this treatment increasing with increasing lipophilicity. Drugs are considered to be lipophilic if the value of logP, a ratio of unionized solute concentrations dissolved in 2 solutions (octanol and water), is > 1.0.18 Because minoxidil has a logP of 1.33, the dog of the present report was considered a reasonable candidate for IVLE after oral exposure to the drug.19 Its blood pressure began to normalize within 2 hours after IVLE administration; however, a dopamine infusion was also being administered concurrently so the component responsible for the normotension remains unclear. Given that dopamine has low lipophilicity (logP, ~0.99), the potential impact of the concurrently administered IVLE on circulating dopamine concentration was considered clinically unimportant.20 Serum minoxidil concentration was not measured before or after IVLE administration, making it difficult to assess the effects of IVLE on systemic minoxidil concentration.

Both ondansetron and maropitant are classified as antiemetics. Whereas ondansetron exerts its effects by antagonizing 5-hydroxytryptamine 3 (serotonin) receptors peripherally, centrally, or both, maropitant inhibits its substance P by antagonizing neurokinin-1 receptors within the CNS.15 Nausea and vomiting are 2 adverse reactions reported for both IVLE and dopamine infusions,15,38 and this could explain the observed episodes of vomiting that warranted administration of ondansetron and maropitant.

The owner’s personal finances were a limiting factor in our ability to thoroughly evaluate and manage the dog of the present report. Echocardiography was recommended to screen for the well-described cardiovascular lesions secondarily associated with minoxidil, but was declined by the owner. Various ECG changes have been identified in humans with minoxidil overdose, including ST segment depression, T-wave flattening, and T-wave inversion.3,9-12,1 The changes have been suggested to represent ischemic injury secondary to the tachycardia-induced increase in myocardial oxygen demand and decrease in coronary perfusion caused by profound systemic hypotension.2,12 Although the dog was not evaluated by a board-certified cardiologist, the ECG findings were otherwise unremarkable aside from the previously noted suspected supraventricular tachycardia.

Various cardiac biomarkers have also been measured in case reports11 of humans with minoxidil overdose to test for myocardial infarction. Cardiac troponin assays are used to assess myocardial cell injury and necrosis in veterinary patients, and although the results may be unable to guide treatment, they may assist in prognostication and evaluation of the risk for cardiovascular-related death in dogs with suspected myocarditis or myocardial injury.21 No such assay was performed for the dog of the present report owing to financial limitations; however, it would be reasonable to test for the presence and severity of myocardial injury in future veterinary cases of minoxidil toxicosis.

The manufacturer of an oral minoxidil formulation prescribed for humans with refractory hypertension recommends concurrent prescription of β-blockers and loop diuretics when the minoxidil product is prescribed to prevent reflex tachycardia, an increase in myocardial oxygen demand, and volume overload.8 Judicious use of IV fluid therapy has been advocated for patients with minoxidil overdose owing to concerns of precipitating congestive heart failure.6 In contrast, IV fluid therapy may facilitate urine production and promote renal excretion of minoxidil.6

The dog of the present report was mildly azotemic with mild hyperlactatemia at initial evaluation. These findings were interpreted as secondary to dehydration from emesis, renal hypoperfusion from hypotension, or both. However, without further diagnostic testing of cardiac function, and in consideration that whole-blood lactate concentration returned to within reference limits by 6 hours after hospital admission, no additional IV fluid therapy was pursued after administration of the initial fluid bolus owing to concerns of precipitating signs of volume overload.

The dog of the present report was successfully treated for minoxidil toxicosis after ingestion of an over-the-counter topical hair growth promoter containing 5% minoxidil foam. Because no measurement of serum minoxidil concentrations was performed at any point and because dopamine and IVLE were administered concurrently, the specific treatment com-
ponents that contributed to this successful outcome remain unknown. In an ideal situation, diagnostic testing, including echocardiography, a cardiac troponin assay, and ECG evaluation by a board-certified cardiologist, would have been performed to determine whether myocardial injury had occurred. Given the widespread commercial availability of minoxidil, it is important for veterinarians to be aware of this drug’s toxic properties. Owing to the potential need for intensive monitoring and advanced treatments, referral of clinically affected veterinary patients to a specialty facility appears reasonable and appropriate.

Footnotes
a. Men’s Rogaine unscented foam, Johnson & Johnson, Skillman, NJ.
b. Critical Care Xpress, NOVA Biomedical, Waltham, Mass.
d. Dopamine hydrochloride injection USP, Hospira Inc, Lake Forrest, III.
e. Intralipid 20%, Fresenius Kabi, Uppsala, Sweden.
f. Esmolol hydrochloride injection, Fresenius Kabi, Lake Zurich, Ill.
g. Ondansetron injection, Fresenius Kabi, Lake Zurich, Ill.
h. Cerenia, Zoetis, Kalamazoo, Mich.

References