Suspected tolazoline toxicosis in a llama

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A 4-year-old 140-kg (310-lb) female llama (Lama glama) was evaluated at the Western College of Veterinary Medicine Teaching Hospital because of a swollen medial digit on the left hind limb that was first detected 2 weeks earlier. The only abnormality detected during physical examination was a warm, firm swelling associated with a draining tract centered over the proximal interphalangeal joint of the medial left hind digit. To obtain radiographs and further examine the swelling, the llama was sedated with xylazine hydrochloride (0.5 mg/kg [0.23 mg/lb] of body weight, IM). Soft-tissue swelling, gas pockets, and a moderate periosteal reaction on the first and second phalanges of the medial digit were detected on radiographs. These findings were consistent with a diagnosis of abscess. Approximately 25 minutes after the first xylazine injection, an additional 70 mg of xylazine was given IV to facilitate debridement and flushing of the wound. A penrose drain was placed, and the foot was bandaged.

Approximately 40 minutes after administration of the second dose of xylazine, the llama was given tolazoline hydrochloride (4.3 mg/kg [2.0 mg/lb]). The dose of tolazoline used was determined on the basis of the dose suggested by the manufacturer, which was determined from results of studies done on horses. Half the dose was to be slowly injected IV and the other half IM. However, the full dose was erroneously injected into the jugular vein. Xylazine-induced sedation was effectively reversed within minutes, and the llama became weak and recumbent. Physical examination revealed the temperature, pulse, and respiratory rate to be similar to values determined during initial examination. We suspected that the llama had become sedated again from residual xylazine, so an additional 300 mg of tolazoline was administered (150 mg, IV; 150 mg, IM). Within 3 minutes, the llama made an attempt to stand but then returned to sternal recumbency. Ten minutes after the second dose of tolazoline, the llama developed signs of anxiety, started trembling, and became hyperesthetic around the head and neck. Profuse salivation and tachypnea (> 80 breaths/min) with episodes of dyspnea were observed. Mucous membranes remained pink, capillary refill time was < 2 seconds, and abnormalities were not detected during thoracic and abdominal auscultation. A catheter was placed into the right jugular vein to provide venous access in anticipation of further problems, and lactated Ringer's solution was administered at a rate of 10 mL/kg/h (+5 mL/lb/h). Results of arterial blood gas analysis revealed a partially compensated respiratory alkalosis attributable to hyperventilation (pH = 7.546; PaCO2 = 23.0 mm Hg; bicarbonate concentration = 19.6 mmol/L; base excess = 0.9 mmol/L; PaO2 = 115.1 mm Hg). Results of plasma electrolyte analysis revealed mild hypokalemia (potassium concentration = 2.96 mmol/L; reference range, 3.7 to 7.8 mmol/L), so potassium chloride (20 mEq/L) was added to the lactated Ringer's solution. Although PaO2 was considered adequate, a 12-F insufflation catheter was advanced into one ventral nasal meatus to the level of the medial canthus of the eye, and 10 L of 100% oxygen/min was administered.

Thirty minutes after administration of the second dose of tolazoline, the llama began to convulse, and diazepam (0.07 mg/kg [0.03 mg/lb], IV) was rapidly administered. Treatment with diazepam controlled seizure activity. However, over the next 60 minutes, 2 more seizures developed that required treatment with diazepam. During the first seizure, peripheral pulses became weaker until they were no longer palpable. A base-apex ECG revealed sinus tachycardia with a heart rate of 160 beats/min. Arterial blood pressures were measured, using an oscillometer. The appropriately sized cuff (ie, cuff width was 40% of limb circumference) was placed around the right antebrachium, and the llama was maintained in sternal recumbency with the blood pressure cuff at the level of the heart. Systolic arterial pressure (SAP) was 50 mm Hg, diastolic arterial pressure (DAP) was 22 mm Hg, and mean arterial pressure (MAP) was 32 mm Hg. Heart rate recorded on the oscillometer matched that obtained by thoracic auscultation, and repeated measurements were similar, so we considered that the measured indirect blood pressures were accurate. Lactated Ringer's solution was infused under pressure, and a phenylephrine infusion (2 µg/kg/min [0.9 mg/lb/min], IV) was started, using a syringe driver. Peripheral pulses became palpable, and within minutes of commencing the phenylephrine infusion, indirect SAP
increased to 130 mm Hg, DAP to 30 mm Hg, and MAP to 50 mm Hg. Results of a second arterial blood gas analysis indicated continued hyperventilation but with a greater degree of metabolic acidosis, likely from decreased peripheral perfusion during the hypotensive crisis (pH = 7.360; PaCO₂ = 28.0 mm Hg; bicarbonate concentration = 15.9 mmol/L; base excess = –7.8 mmol/L; PaO₂ = 76.5 mm Hg; potassium concentration = 2.28 mmol/L). Based on the inspired oxygen concentration, PaO₂ was considered low, so nasal insufflation of oxygen was continued. During this time, the llama began sweating, and its skin became flushed and warm to the touch, although rectal temperature was only 36.2°C (97.3°F).

The llama developed profuse diarrhea 75 minutes after administration of the second dose of tolazoline (45 minutes after initiating the phenylephrine infusion), and subsequent auscultation of the abdomen revealed a hypermotile gastrointestinal tract. The phenylephrine infusion was discontinued, and the llama gradually became more aware of its surroundings and was able to hold up its head and neck and remain in sternal recumbency without assistance. Indirect blood pressure was stable without the phenylephrine infusion.

Minutes later, the llama became severely dyspneic and collapsed. An upper airway obstruction was diagnosed and attributed to nasal edema. The nasal catheter was removed, phenylephrine spray was administered into each nasal cavity, and nasal intubation was attempted, using a 9-mm endotracheal tube. However, because of the extremely congested and edematous nasal passages, nasal intubation was unsuccessful. An emergency tracheotomy was performed, and 100% oxygen was administered at a rate of 3 L/min via the tracheotomy tube, using a breathing circuit and anesthetic machine. Indirect SAP measured at this time was 100 mm Hg, DAP was 40 mm Hg, and MAP was 60 mm Hg. Heart rate was 120 beats/min. Oxygen delivery was discontinued after 45 minutes, although the tracheotomy tube was left in place.

Two hours after the second tolazoline injection, no further abnormalities had developed, and the llama was able to maintain itself in sternal recumbency. Arterial oxygen concentrations remained acceptable (>90 mm Hg) with the llama breathing room air. Over the 2 hours of aggressive treatment, the llama had received approximately 15 L of lactated Ringer’s solution. The llama remained in sternal recumbency for the following 2 hours while it was warmed with heating pads, and it was taken back to its stall and monitored for the next 12 hours; further signs of respiratory distress or other problems did not develop. The following day, the tracheotomy tube was removed, and the llama was discharged from the hospital. On follow-up examinations 4 and 6 days later, the tracheotomy site and hind limb wound were found to be healing normally.

Llamas frequently require veterinary attention for medical and surgical problems, and depending on the patient’s temperament and the procedure, variable levels of sedation may be required. Of the α₂-adrenoceptor agonists that are used to maintain recumbency and provide sedation, analgesia, and muscle relaxation, xylazine is the most commonly used agent in llamas. Typical doses of xylazine range from 0.11 to 1.0 mg/kg (0.05 to 0.45 mg/lb) given IV or IM depending on the level and duration of sedation desired. Xylazine at doses of 0.4 to 0.6 mg/kg (0.18 to 0.27 mg/lb) administered IV usually results in 30 to 45 minutes of recumbency; whereas the sedative effects can last up to 2 hours. Although camels are not ruminants, they appear to respond to xylazine in a similar manner; adverse effects include bradycardia, centrally-mediated hypotension, and decreased gastrointestinal tract motility. During prolonged periods of recumbency, ruminants and camels are at risk of bloat, regurgitation, and aspiration. The use of α₂-adrenoceptor antagonists has, therefore, become a popular and effective means of shortening the recovery period after xylazine sedation and can reduce the incidence of adverse effects. There are several α₂-adrenoceptor antagonists available for use in animals, and tolazoline has been shown to be an effective reversal agent for use in ruminants. Tolazoline is an imidazoline derivative with mixed pharmacologic properties, and although its α₂-adrenoceptor antagonist effects predominate, tolazoline also has α₂-adrenoceptor agonist, cholinergic receptor agonist and antagonist, and H₁ and H₂ histamine receptor agonist and antagonist properties. The most frequently reported adverse effects are tachycardia, histaminic-mediated hypotension, and cholinergic-stimulated gastrointestinal tract hypermotility, which develop most commonly after rapid IV administration. To slow the time to peak plasma concentration and hopefully minimize adverse effects, half the calculated dose can be given IV and half IM. Tachycardia, hypotension, and gastrointestinal tract hypermotility were observed in the llama of this report, and tolazoline toxicosis was the retrospective diagnosis.

The first abnormal sign observed was generalized weakness when the llama became recumbent approximately 45 minutes after administration of the first dose of tolazoline. Our initial suspicion was that weakness was attributable to incomplete reversal of xylazine. In theory, this could occur if tolazoline was rapidly metabolized and eliminated while enough xylazine remained in the circulation to elicit an effect. Another possibility was that weakness and depressed mentation were the result of tolazoline-induced hypotension and decreased cerebral blood flow. In puppies, when tolazoline-induced hypotension resulted in a decrease in MAP > 20% from baseline, there was a resultant decrease in cerebral blood flow. However, it is unlikely that tolazoline-induced hypotension was the cause of the depressed mentation seen in this llama, because peripheral pulses were readily palpable prior to administration of the second dose of tolazoline.

The second dose of tolazoline appeared to be responsible for the rapid deterioration in physical status. Following the second dose, the llama developed signs of anxiety and began trembling, sweating, and salivating excessively. Tolazoline increases production of secretions by the salivary, lacrimal, and sweat glands. Signs of anxiety may have developed as a result of abdominal pain that was attributable to tola-
tolazoline-induced gastrointestinal tract hypermotility. Gastrointestinal tract hypermotility can result in vomiting and diarrhea; the latter was observed in the llama of this report. Signs of anxiety and seizures may also have developed because of tolazoline-induced CNS stimulation; this has been reported after administration of other α2-adrenoceptor antagonists such as atipamezole.

Tolazoline can cause tachycardia directly, or tachycardia may result from a compensatory reflex to tolazoline-induced hypotension. Although we did not observe cardiac arrhythmias during the period of ECG monitoring, arrhythmias commonly develop as a result of tolazoline toxicosis. Intravenous phenylephrine infusions can successfully reverse profound tolazoline-induced hypotension in humans, and this treatment appeared to be effective for the llama of this report.

To our knowledge, upper-airway obstruction has not been reported as a potential complication of tolazoline overdose. We attributed the obstruction in the llama of this report to nasal edema from histamine release, increased respiratory effort, and a lowered head position during much of the emergency treatment period. Stimulation of nasal secretions by tolazoline may have contributed to tolazoline-mediated blockade of peripheral α2-adrenoceptors, activation of both H1 and H2 histamine receptors, indirect release of histamine, or a combination of these mechanisms. Intravenous phenylephrine infusions can successfully reverse prolonged tolazoline-induced hypotension in humans, and this treatment appeared to be effective for the llama of this report.

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References