Clenbuterol toxicosis in three Quarter Horse racehorses after administration of a compounded product

Jessica A. Thompson, dvm, MS; Mustajab H. Mirza, dvm, MS; Steven A. Barker, PhD; Timothy W. Morgan, dvm, PhD, DACVP; Rudy W. Bauer, dvm, PhD, DACVP; Rebecca S. McConnico, dvm, PhD, DACVIM

Case Description—Three Quarter Horse racehorses were examined for suspected clenbuterol overdose 12 to 24 hours after administration by mouth of a compounded clenbuterol product.

Clinical Findings—All horses developed sinus tachycardia, muscle tremors, hyperhidrosis, and colic. Abnormalities on serum biochemical analysis included hyperglycemia, azotemia, and high creatine kinase activity. The presence of clenbuterol in the serum of all 3 horses and in the product administered was confirmed and quantified by use of liquid chromatography–electrospray tandem mass spectrometry.

Treatment and Outcome—Propranolol (0.01 mg/kg [0.005 mg/lb], IV) was administered to all 3 horses for antagonism of β-adrenergic effects and caused a transient decrease in heart rate in all patients. All horses also received crystalloids fluids IV and other supportive treatment measures. Two horses were euthanatized (2 and 4 days after admission) because of complications. One horse recovered and was discharged 4 days after admission to the hospital. In the 2 nonsurviving horses, skeletal and cardiac muscle necrosis was evident at necropsy, and tissue clenbuterol concentrations were highest in the liver.

Clinical Relevance—Clenbuterol is a β1-adrenergic receptor agonist licensed for veterinary use as a bronchodilator. At doses ≥ 10 µg/kg (4.5 µg/lb), in excess of those normally prescribed, β-adrenergic stimulation by clenbuterol may cause sustained tachycardia, muscle tremors, hyperglycemia, and cardiac and skeletal muscle necrosis. Laminitis, acute renal failure, rhabdomyolysis, and cardiomyopathy were fatal complications associated with clenbuterol overdose in 2 horses in the present report. At the dose administered, propranolol was effective for short-term control of sinus tachycardia, but it did not alleviate all clinical signs in patients in the present report. These cases demonstrated the risks associated with the use of nonsupervised compounded medications for which the ingredients may be unknown. (J Am Vet Med Assoc 2011;239:842–849)

A 482-kg (1,060-lb) 7-year-old sexually intact male Quarter Horse from a racetrack in southern Louisiana was referred to the Veterinary Teaching Hospital at Louisiana State University with a 16-hour history of muscle tremors, hyperhidrosis, colic, and a stiff gait. Clinical signs occurred after administration of a compounded clenbuterol solution that was purported to contain 72.5 µg of clenbuterol/mL. The horse had been receiving the FDA-approved formulation of clenbuterol hydrochloride that is a syrup containing 72 µg of clenbuterol hydrochloride/mL; (0.8 µg/kg [0.36 µg/lb], PO, q 24 h); however, this was the first time the compounded product had been administered. The label on the compounded product did not include clear instructions for administration, and the product was administered to the horse according to oral instructions provided by the seller of the product (0.5 mL/45.5 kg [0.5 mL/100 lb], q 12 h to q 24 h). Minimal information was available about the seller of the compounded product and it was not stated how much of this product the horse had received. Prior to referral, the horse had not responded to treatment with flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IV, once), treatment with acepromazine maleate (unknown dose and route of administration), and administration of an electrolyte solution by mouth. It was not clear whether these treatments were supervised by an attending veterinarian.

On initial examination, the horse had muscle tremors evident over the entire body. The right gluteal and quadriceps muscles were firm, and the horse was unwilling to bear full weight on the right hind limb. Lameness was not altered by perineural anesthesia of the digital nerves of the right hind limb at the level of the distal sesamoid bones. The horse was sweating and tachycardic (heart rate, 96 beats/min), and capillary refill time was prolonged (5 seconds). The horse was moderately dehydrated on the basis of skin turgor. Nasogastric intubation recovered 7 L of nasogastric reflux, but rectal examination was unremarkable. Abdominal ultrasound revealed dilation of the renal pelvis of the right kidney with decreased corticomedullary definition.

Abbreviation

CVP Central venous pressure

Unauthenticated | Downloaded 12/20/23 07:36 PM UTC
A CBC found hemoconcentration (59.9%; reference range, 32% to 52%), leukocytosis (14.5 × 10³ WBCs/µL; reference range, 6.0 × 10³ WBCs/µL to 9.0 × 10³ WBCs/µL), and thrombocytopenia (92 × 10³ platelets/µL; reference range, 93 × 10³ platelets/µL to 240 × 10³ platelets/µL), and a serum biochemical analysis indicated high activities of creatine kinase (101,400 U/L; reference range, 0 to 350 U/L) and aspartate aminotransferase (endpoint not reported because of analyzer interference from marked increase in AST activity), azotemia (32 mg/dL; reference range, 12 to 26 mg/dL), hyperbilirubinemia (6.9 mg/dL; reference range, 0.3 to 2.5 mg/dL), hyperglycemia (484 mg/dL; reference range, 70 to 105 mg/dL), hyponatremia (124 mmol/L; reference range, 130 to 140 mmol/L), and hypochloremia (77 mmol/L; reference range, 97 to 105 mmol/L). Urinalysis revealed isosthenuria, aciduria, glucosuria, and a large amount of myoglobin.

Emergency treatment consisted of methocarbamol (12 mg/kg [5.45 mg/lb], IV, once), rapid IV infusion of crystalloid fluids (10 L/h), insulin (0.25 U/kg [0.11 U/lb] IM, once), unfractionated heparin (40 U/kg [20 U/lb], SC, q 8 h), and butyrophanol tartrate (0.04 mg/kg [0.018 mg/lb], IV, once). Following the initial infusion, IV administration of a balanced electrolyte solution (4 mL/kg/h [1.82 mL/lb/h]), supplemented with calcium borogluconate (14 mg/kg [6.36 mg/lb/h]), potassium chloride (0.08 mEq/kg/h [0.036 mEq/lb/h]), and d-methyl sulfoxide (1 g/kg [0.45 g/lb] in 10% solution, once) was continued. Despite transient improvement, the horse became increasingly agitated and appeared uncomfortable. Phenylbutazone (4.4 mg/kg [2 mg/lb], IV, once), xylazine (0.3 mg/kg [0.15 mg/lb], IV, once), and butyrophanol (0.01 mg/kg [0.005 mg/lb], IV, once) failed to relieve signs of pain.

Within 8 hours of admission, the horse became recumbent. Gluteal, quadriceps, and epaxial muscle groups were firm bilaterally, and whole body muscle tremors continued. Tachycardia (112 beats/min) persisted, and the systolic heart murmur became less pronounced. Sweating and anxiety were subjectively decreased, but no effect on muscle stiffness was observed.

During the evening of day 2, the horse's condition had deteriorated further. Neurologic abnormalities included loss of coordinated motor activity in the rear limbs, absent menace responses, sluggish direct pupillary light reflexes, and development of nystagmus after repositioning. Tachycardia and sweating persisted, and the horse's body temperature had decreased to 34.8°C (94.6°F). Disseminated intravascular coagulation was suspected on the basis of thrombocytopenia and prolonged prothrombin (13.2 seconds; reference range, 8 to 10 seconds) and partial thromboplastin times (60.6 seconds; reference range, 32 to 42 seconds). Azotemia and electrolyte abnormalities had not resolved despite aggressive IV fluid therapy.

The compounded product believed to have caused this patient's clinical signs was confirmed on day 2 as pure clenbuterol by use of electrospray tandem mass spectrometry. The concentration of clenbuterol in this product was determined to be 5.0 mg/mL, which is approximately 70 times the concentration in the FDA-approved product.6 Clenbuterol was also detected in a sample of the horse's serum which was obtained at admission, at a concentration of 5.45 ng/mL. With definitive evidence of clenbuterol toxicosis, propranolol (0.01 mg/kg) was subsequently administered in 150 mL of saline (0.9% NaCl solution) as an IV infusion over 30 minutes. After the propranolol administration, the horse's heart rate decreased from 90 to 60 beats/min, and the systolic heart murmur became less pronounced. Sweating and anxiety were subjectively decreased, but no effect on muscle stiffness was observed.

On day 3 of hospitalization, reevaluation of neurologic, renal, and musculoskeletal abnormalities revealed further deterioration. The owners elected euthanasia, and the horse was euthanatized by IV administration of an overdose of barbiturates approximately 50 hours after clenbuterol ingestion.

At necropsy, the muscles of the upper pelvic limbs contained multifocal to coalescing areas of abnormally firm, pale pink to white discoloration bilaterally. Histologically, these muscles had multifocal to coalescing necrosis of myocytes, affecting individual fibers as well as large muscle bundles. Skeletal myocyte necrosis was characterized by hypercontractility, cytoplasmic vacuolization, loss of cellular detail, swollen myofibers, and loss of cross-striations. Hypaxial muscles were diffusely

---

1. Emergency treatment consisted of methocarbamol (12 mg/kg [5.45 mg/lb], IV, once), rapid IV infusion of crystalloid fluids (10 L/h), insulin (0.25 U/kg [0.11 U/lb] IM, once), unfractionated heparin (40 U/kg [20 U/lb], SC, q 8 h), and butyrophanol tartrate (0.04 mg/kg [0.018 mg/lb], IV, once). Following the initial infusion, IV administration of a balanced electrolyte solution (4 mL/kg/h [1.82 mL/lb/h]), supplemented with calcium borogluconate (14 mg/kg [6.36 mg/lb/h]), potassium chloride (0.08 mEq/kg/h [0.036 mEq/lb/h]), and d-methyl sulfoxide (1 g/kg [0.45 g/lb] in 10% solution, once) was continued. Despite transient improvement, the horse became increasingly agitated and appeared uncomfortable. Phenylbutazone (4.4 mg/kg [2 mg/lb], IV, once), xylazine (0.3 mg/kg [0.15 mg/lb], IV, once), and butyrophanol (0.01 mg/kg [0.005 mg/lb], IV, once) failed to relieve signs of pain.

2. Analysis of IV fluids continued but was amended to include Salmonella typhimurium antisepticum of equine origin (total dose, 1 L, IV [0.5 L/h]) and 6% hetastarch (1 mL/kg/h, constant rate infusion for 3 hours, IV), and calcium supplementation IV was discontinued, but hypertonic saline (7% NaCl) solution (2 mL/kg/h [0.91 mL/lb/h] for 1 hour) was added to the balanced electrolyte solution. Heparin treatment was discontinued, and naloxyone hydrochloride (0.016 mg/kg [0.008 mg/lb], IV, once), acepromazine (0.06 mg/kg [0.03 mg/lb], IM, q 6 h), furosemide (0.5 mg/kg [0.23 mg/lb], IV, once), and dexamethasone sodium phosphate (0.04 mg/kg [0.004 mg/lb], IV, once) were administered.

3. Analgesia was attempted with butyrophanol (0.9 mg/kg [0.4 mg/lb], IM, once), xylazine (0.44 mg/kg [0.2 mg/lb], IV, once), detomidine (0.2 mg/kg [0.09 mg/lb], IV, once), and guaifenesin (11.1 mg/kg [5.0 mg/lb], IV, once). A constant rate infusion of butyrophanol (0.013 mg/kg/h [0.006 mg/lb/h], IV) with periodic administration of diazepam (0.1 to 0.2 mg/kg [0.05 to 0.09 mg/lb], IV, as needed) and detomidine provided adequate sedation to prevent self-injury. Additional supportive care included urinary catheterization, heavy bedding, manual repositioning, eye lubrication, and placement of protective headgear and lower limb bandages.

4. By the evening of day 2, the horse's condition had deteriorated further. Neurologic abnormalities included loss of coordinated motor activity in the rear limbs, absent menace responses, sluggish direct pupillary light reflexes, and development of nystagmus after repositioning. Tachycardia and sweating persisted, and the horse's body temperature had decreased to 34.8°C (94.6°F). Disseminated intravascular coagulation was suspected on the basis of thrombocytopenia and prolonged prothrombin (13.2 seconds; reference range, 8 to 10 seconds) and partial thromboplastin times (60.6 seconds; reference range, 32 to 42 seconds). Azotemia and electrolyte abnormalities had not resolved despite aggressive IV fluid therapy.

5. The compounded product believed to have caused this patient's clinical signs was confirmed on day 2 as pure clenbuterol by use of electrospray tandem mass spectrometry. The concentration of clenbuterol in this product was determined to be 5.0 mg/mL, which is approximately 70 times the concentration in the FDA-approved product. Clenbuterol was also detected in a sample of the horse's serum which was obtained at admission, at a concentration of 5.45 ng/mL. With definitive evidence of clenbuterol toxicosis, propranolol (0.01 mg/kg) was subsequently administered in 150 mL of saline (0.9% NaCl solution) as an IV infusion over 30 minutes. After the propranolol administration, the horse's heart rate decreased from 90 to 60 beats/min, and the systolic heart murmur became less pronounced. Sweating and anxiety were subjectively decreased, but no effect on muscle stiffness was observed.

6. During the evening of day 2, dexamethasone (0.04 mg/kg, IV), omeprazole (0.5 mg/kg, IV, q 24 h), and ceftiouf sodium (2.2 mg/kg [1.0 mg/lb], IM, q 12 h) were administered. Transdermal lantentary patches (0.67 µg/µg/h [0.3 µg/µg/h]) were applied. Fluid therapy IV was administered to stimulate diuresis with a balanced polyionic solution, supplemented with magnesium sulfate (2 mg/kg/h), potassium chloride (0.08 mEq/kg/h), and hypertonic saline solution (2 mL/kg/h for 1 hour) for 6 hours.

On day 3 of hospitalization, reevaluation of neurologic, renal, and musculoskeletal abnormalities revealed further deterioration. The owners elected euthanasia, and the horse was euthanatized by IV administration of an overdose of barbiturates approximately 50 hours after clenbuterol ingestion.

At necropsy, the muscles of the upper pelvic limbs contained multifocal to coalescing areas of abnormally firm, pale pink to white discoloration bilaterally. Histologically, these muscles had multifocal to coalescing necrosis of myocytes, affecting individual fibers as well as large muscle bundles. Skeletal myocyte necrosis was characterized by hypercontractility, cytoplasmic vacuolization, loss of cellular detail, swollen myofibers, and loss of cross-striations. Hypaxial muscles were diffusely.
swollen, soft, and mottled with dark red, patchy to coalescing areas of hemorrhage. Myocyte necrosis, characterized by hyper eosinophilia, fragmentation of muscle fibers, loss of cellular detail, loss of cross-striations, and muscle fiber loss, was evident histologically (Figure 1). Frequent blood clots, characterized by large areas of hemorrhage containing fibrin and inflammatory cells, were also evident in the hypaxial muscles.

Although not grossly abnormal, the myocardium was necrotic on histologic examination. Degenerate to necrotic cardiomyocytes were evident as scattered individual cells and in small clusters, characterized by myofiber fragmentation, hyper eosinophilia, cytoplasmic granularity, and occasional loss of cross-striations (Figure 2). Multifocal interstitial edema and focal sub-endocardial hemorrhage were present.

The bladder contained reddish-brown, cloudy urine. Mild to moderate renal tubular degeneration and necrosis were present in the renal cortex, characterized by individual hyper eosinophilic cells with loss of nuclear detail, sloughed pyknotic cells within the tubular lumen, and the occasional presence of flattened epithelial cells lining renal tubules. In the tubules of the cortex and medulla, accumulation of eosinophilic, proteinaceous globules and red, granular casts was widespread. With the postmortem confirmation of rhabdomyolysis, the kidney lesions were considered to be consistent with acute renal failure because of pigment nephropathy.

Moderate, diffuse, hepatic hemosiderosis and pulmonary congestion and edema with severe hemosiderosis were also present. Abnormalities in the lungs, liver, and heart were compatible with acute heart failure or acute cardiac insufficiency.

The samples of liver and kidney obtained postmortem, approximately 48 hours after clenbuterol administration, as well as the serum sample obtained 24 hours after administration, were analyzed for the presence of clenbuterol residues by use of liquid chromatography–electrospray tandem mass spectrometry. All samples were positive for the presence of clenbuterol, with tissue concentrations being markedly higher than serum concentration. Clenbuterol in serum 24 hours after ingestion was present at a concentration of 5.45 ng/mL. At 48 hours after ingestion, clenbuterol was detected in the liver at a concentration of 376.89 ng/mL and in the kidney at a concentration of 202.24 ng/mL.

A 516-kg (1,135-lb) 2-year-old racing Quarter Horse filly from the same racetrack as the first horse was examined approximately 24 hours after administration by mouth of an unknown amount of the same compounded clenbuterol product as horse 1. Excitation, hyperhidrosis, and muscle tremors were noted by caretakers shortly after administration. Treatments by the caretakers prior to admission to the hospital included an unknown amount of methocarbamol, milk of magnesia, valerian root, and buttermilk. A referring veterinarian administered acepromazine (0.06 mg/kg, IM, once), dexamethasone (0.04 mg/kg, IV and IM, once each), flunixin meglumine (1.1 mg/kg, IM, once), and 8 L of crystalloid fluids IV prior to referral for suspected colic.

Abnormalities on examination at the Veterinary Teaching Hospital included tachycardia (112 beats/min), hyperhidrosis, muscle tremors, and subcutaneous emphysema in the pectoral region. Electrocardiography confirmed sinus tachycardia. Central venous pressure, measured with a water manometer via a catheter placed...
in the right jugular vein, was increased at 22 cm H$_2$O (reference range, 5 to 10 cm H$_2$O).

Results of a CBC were unremarkable, and a serum biochemical analysis revealed hyperglycemia, azotemia, hyperbilirubinemia, hypocalcemia, hyperphosphatemia, hypochloremia, and high creatine kinase activity. Serum clenbuterol concentration, measured by use of liquid chromatography–electrospray tandem mass spectrometry, was found to be 0.80 ng/mL.

Rapid IV infusion of 10 L of balanced crystalloid fluids supplemented with calcium borogluconate (90 mg/kg [40.9 mg/lb/h]), potassium chloride (0.4 mEq/kg/h [0.18 mEq/lb/h]), magnesium sulfate (20 mg/kg/h [9.1 mg/lb/h]), and dimethyl sulfoxide (1 g/kg/h) was administered, followed by hypertonic saline solution (500 mL, IV, once). Propranolol (0.01 mg/kg, IV, once), diluted in 150 mL of saline solution, was administered over 30 minutes. After propranolol administration, the horse's heart rate decreased to 64 beats/min, and the CVP decreased to 15 cm H$_2$O. The muscle tremors remained. Butorphanol (0.03 mg/kg [0.013 mg/lb], IM, once), omeprazole (4.4 mg/kg, PO, q 24 h), and insulin (0.22 U/kg [0.1 U/lb], IM, once) were administered, and molded frog support pads were applied to all 4 feet. Intravenous fluid therapy was maintained with IV administration of a balanced electrolyte solution (4 mL/kg/h) supplemented with calcium borogluconate (14 mg/kg/h), potassium chloride (0.08 mEq/kg/h), and magnesium sulfate (2 mg/kg/h). Cefetiofur sodium (2.2 mg/kg, IV, q 12 h) was also administered because of the potential risk for cellulitis of the pectoral region.

On day 2 of hospitalization, sinus tachycardia (64 beats/min) and muscle tremors were still present, and a transient fever (38.5°C [101.4°F]) was noted. A repeated serum biochemical analysis revealed resolution of hyperphosphatemia, hypocalcemia, and hypochloremia; less severe hyperglycemia, azotemia, and hyperbilirubinemia; and decreased creatine kinase activity. Thrombin time and partial thromboplastin time were mildly prolonged, but no clinical signs of coagulopathy were observed. Insulin (0.12 U/kg [0.05 U/lb], SC, once) administration was repeated, and supportive care was continued.

By day 3 of hospitalization, blood glucose concentration was within the reference range; the azotemia had resolved, and the horse's heart rate had returned to within normal limits (40 to 48 beats/min). The pectoral subcutaneous emphysema had resolved, and no clinical signs of laminitis had developed despite the presence of mild digital pulses in the front feet. Intravenous fluid therapy was discontinued on the fourth day of hospitalization, and the patient was eating, drinking, defecating, and urinating appropriately. A serum biochemical analysis on day 4 of hospitalization revealed residual increases in total bilirubin concentration and activities of creatine kinase, aspartate aminotransferase, and alkaline phosphatase.

The horse was discharged after 5 days of hospitalization with no medications required. All clinical signs and clinicopathologic abnormalities had resolved at the time of discharge; although mildly increased digital pulses were still present. This horse went on to have a successful racing career and was still competing in 2010.

A 533-kg (1,173-lb) 3-year-old Quarter Horse gelding (horse 3), which was in race training and housed at the same barn as the first 2 horses described, was evaluated at the Veterinary Teaching Hospital for treatment of muscle tremors, profuse sweating, and tachycardia following administration by mouth of an unknown amount of the same compounded clenbuterol product as horse 1 and 2, 24 hours prior to admission. Flunixin meglumine (1.1 mg/kg, IV, twice), acepromazine (0.06 mg/kg, IM, once), dexamethasone (0.04 mg/kg, IV and IM, once each), lactated Ringer's solution (1 L, IV, once), and methocarbamol (20 mg/kg, PO, once) were administered by the referring veterinarian. Valerian root and milk of magnesia were given by the horse’s caretaker.

On initial examination, sinus tachycardia (84 beats/min), mild hypothermia (36.9°C [98.4°F]), profuse sweating, prolonged capillary refill time (3 seconds), and whole body muscle tremors were detected. The quadriceps muscles were firm to the touch. Central venous pressure was 7 cm H$_2$O when measured via the right jugular vein, suggesting hypovolemia in view of other clinical signs (and accounting for slight measurement error). Initial treatment included rapid IV infusion of 10 L of balanced crystalloid fluids, supplemented with calcium borogluconate (90 mg/kg/h), potassium chloride (0.4 mEq/kg/h), and magnesium sulfate (20 mg/kg/h). Colloid solution, 6% hetastarch (1mL/kg/h constant rate infusion for 2 hours), and hypertonic saline solution, (2 mL/kg/h for 0.5 hours) were administered IV concurrently.

Hyperglycemia, azotemia, hyperbilirubinemia, hyperphosphatemia, hypochloremia, and high activities of creatine kinase, aspartate aminotransferase, and alkaline phosphatase were present on a serum biochemical analysis. A CBC was unremarkable. Urinalysis revealed isohenuria, glucosuria, a large amount of blood suspected to be myoglobin, and trace proteinuria and ketonuria.

After fluid resuscitation, the horse's CVP increased to 26 cm H$_2$O, and the horse became more agitated and tachycardic. Propranolol (0.1 mg/kg), diluted in 150 mL of saline solution, was administered IV over 30 minutes. The horse's heart rate, CVP, and agitation decreased after propranolol administration, but the muscle tremors and sweating continued. Insulin (0.22 U/kg, IM, once), butorphanol (0.028 mg/kg [0.013 mg/lb], IM, q 8 h), heparin (19 U/kg [8 U/lb], SC, q 6 h), and omeprazole (1.1 mg/kg, PO, q 24 h) were administered, and frog support pads were applied to the front feet. Intravenous fluid therapy was with a balanced electrolyte solution (4 mL/kg/h) supplemented with calcium borogluconate (14 mg/kg/h), potassium chloride (0.08 mEq/kg/h), magnesium sulfate (20 mg/kg/h), and dimethyl sulfoxide (1 g/kg/h) in 10% solution, once.  

On day 2 of hospitalization, the tachycardia (76 beats/min) and muscle tremors were still present, and mild pyrexia (38.6°C [101.3°F]) developed. Reevaluation of clinicopathologic parameters revealed resolution of hyperphosphatemia. Hyperglycemia, azotemia, hypochloremia, and high creatine kinase activity persisted, and activities of aspartate aminotransferase and alkaline phosphatase had increased since admission. A left shift...
(1,000 band neutrophils/µL) was evident on the CBC, despite a total leukocyte count (5,600 leukocytes/µL and absolute neutrophil count (3,200 neutrophils/µL) within the reference range. Clotting times (prothrombin time, 12.6 seconds; partial thromboplastin time, 44.9 seconds) were mildly prolonged. Propranolol administration was repeated and successfully decreased the heart rate by approximately 10 beats/min. Insulin administration (19 U/kg, SC, once) was also repeated, and all other treatment was continued.

The horse subsequently developed mild bilateral forelimb lameness that progressed to signs of acute laminitis by the end of day 2, despite application of ice to the forefeet. Tripelennamine† (0.75 mg/kg [0.34 mg/lb], IM, once), flunixin meglumine‡ (0.5 mg/kg, IV, once), and pentoxifylline§ (7 mg/kg [3.2 mg/lb], diluted in 1 L of saline solution, IV, q 8 h) were given. Repeated serum biochemical analysis revealed resolution of hyperglycemia and decreasing azotemia.

On the third day of hospitalization, the horse showed signs of acute laminitis in all 4 feet, and muscle tremors persisted. No displacement of the distal phalanx was evident on lateral and dorsopalmar radiographs of all 4 feet. Rectal temperature (38.6°C), heart rate (88 beats/min), and respiratory rate (32 breaths/min) were all increased. Perineural anesthesia of the digital nerves of all 4 limbs produced a temporary decrease in heart rate. Serum biochemical abnormalities had resolved, with the exception of azotemia and elevated activities of aspartate aminotransferase, alkaline phosphatase, and creatine kinase. Mild leukopenia and neutropenia developed, and a persistent left shift was present.

Phenylbutazone (4.4 mg/kg, IV, q 24 h) and butorphanol (0.036 mg/kg [0.025 mg/lb], IM, once) were administered. Furosemide, lower limb support bandages, and ice were applied to all 4 limbs. Under heavy sedation, the horse was placed in a sling. Muscle fasciculations ceased when the horse was non-weight bearing and supported in the sling. A constant rate infusion of ketamine hydrochloride (0.4 mg/kg/h, IV) was initiated with the horse sedated and continued while the horse was in the sling. Administration of crystalloid fluids IV and other medications was continued. Feces became soft on day 3; di-trioctahedral smectite was administered.

By the morning of day 4 of hospitalization, the patient was still tachycardic (80 beats/min). A CBC revealed mild neutropenia, with a degenerative left shift lymphopenia, and monocytosis. Elevations in serum activities of aspartateaminotransferase, alkaline phosphatase, and creatine kinase persisted, and hypocalcemia, hyperbilirubinemia, and hypoproteinemia were detected. Twelve hours later, after slight improvement, the horse was removed from the sling. However, immediate clinical signs of deterioration were evident, including recurrence of tachycardia, tachypnea, and muscle tremors. The oral mucous membranes were congested, and a fever (39.1°C [102.4°F]) developed.

On the fifth day of hospitalization, the patient was febrile (39.1°C [102.4°F], tachycardic (72 beats/min) and severely tachypneic (84 beats/min), with red, injected mucous membranes and a capillary refill time of 3.5 seconds. The horse continued to have signs of laminitis. Unilateral serosanguinous discharge was also noted from the left nostril. Thoracic ultrasonographic findings were consistent with pleuropneumonia. Comet tail artifacts were diffusely distributed throughout the cranial lung fields bilaterally, and bilateral pulmonary consolidation was evident cranioventrally. Bilateral, anechoic pleural effusion (≤1 cm) was present cranioventrally, and pericardial effusion was also identified.

Clinicopathologic reevaluation revealed hyperbilirubinemia, persistently high aspartateaminotransferase and alkaline phosphatase activities, hypophosphatemia, and hypoproteinemia. Creatine kinase activity had decreased greatly and was almost within the reference range. Hyperfibrinogenemia and neutrophilic leukocytosis with a left shift were present. Euthanasia was performed at the owner’s request, and the horse was euthanatized by IV administration of an overdose of barbiturates.

At necropsy, multiple skeletal muscle lesions in this patient were limited to diffuse, small, multifocal areas of myocyte mineralization in hypaxial muscles. When the heart was examined, the myocardium of the ventricular free walls and interventricular septum was diffusely and asymmetrically discolored by pale tan streaking, with the left ventricular free wall being the most severely affected. Approximately 40% of the heart had tan discoloration grossly, and 25% of sections examined microscopically had cardiomyocyte necrosis or inflammatory changes. On histologic examination, cardiomyocyte necrosis was characterized by loss of cross-striations and fragmentation, cellular vacuolization, karyolysis, nuclear pyknosis, and sarcolemmal sheath collapse. Perivascular tissue and areas of the myocardium surrounding Purkinje cells were expanded with granulomatous infiltrate and either nonstaining fluid or a basophilic, mucinous material. Approximately 200 mL of dark yellow fluid was present in the pericardial sac. Aerobic bacterial culture of pericardial fluid did not yield any growth. Subcapsular petechial hemorrhage was observed in the kidneys bilaterally. Nonspecific degenerate and necrotic lesions were identified in the renal tubules, along with evidence of tubular epithelial repair. The bladder contained normal-appearing urine.

The cranioventral region of both lungs was sharply demarcated by dark green consolidation, encompassing about 20% of the lung parenchyma, and the remaining lung tissue was rubbery and partially collapsed. Interlobular spaces in the consolidated area were expanded with edema and yellow, friable material consistent with fibrin, and the pleural surface was covered by a thin layer of similar brown, friable material. The trachea and bronchi were filled with clear to white foam. Aerobic bacterial culture of affected lung yielded a mixed population of Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp, and Proteus spp, consistent with aspiration pneumonia. Histologically, parenchymal necrosis, edema, vascular necrosis, and supplicative exudate were evident in the cranioventral lungs, and large numbers of chain-forming cocci were present in necrotic foci. Neutrophilic infiltration was identified in the adventia and mucosa of the trachea.
The liver was firm with an accentuated lobular pattern on gross examination. Mild vacuolization of centrilobular hepatocytes, mild biliary hyperplasia, and mild lymphocytic infiltration of the portal triads were present. The glandular portion of the stomach was thickened and hyperemic, and about half of the affected area was covered with a fibrinous pseudomembrane that was colonized with coccobacilli. Mild lymphocytic-plasmacytic inflammation was also present in the small intestine and large colon. Laminar edema of the right forefeet and left hind feet was noted, consistent with laminitis. The tissue samples and stomach contents obtained postmortem, approximately 114 hours after clenbuterol administration, as well as the serum sample obtained 24 hours after administration were analyzed for clenbuterol residues by liquid chromatography–electrospray tandem mass spectrometry. All samples were positive for the presence of clenbuterol. Serum clenbuterol concentration 24 hours after administration was 1.05 ng/mL. At 114 hours after administration, clenbuterol was detected in the liver at a concentration of 6.79 ng/mL, in the kidney at 1.70 ng/mL, in the spleen at a concentration of 1.95 ng/mL, in the brain at a concentration of 1.08 ng/mL, and in the stomach contents at a concentration of 1.15 ng/mL.

**Discussion**

In the present report, 3 horses received a severe overdosage of clenbuterol. All horses had prolonged sinus tachycardia, muscle tremors, hyperhidrosis, and hyperglycemia. Complications were severe and included rhabdomyolysis, renal failure, cardiotoxicosis, and laminitis. Propranolol was successful in reducing heart rate in all horses, but it did not alleviate other signs of toxicity. The horse with the lowest serum concentration of clenbuterol at admission survived. The first horse was admitted for clinical signs of colic, and fever was an inconsistent finding in the patients in the present report. Tachycardia, muscle tremors, and sweating were notable on initial examination in all 3 horses. Whereas tachycardia is common in horses with many conditions, including colic, the muscle tremors identified in these horses have also been reported commonly in human patients with symptoms of accidental or intentional clenbuterol overdose.

The horses in the present report were estimated to have received 100 µg/kg (45.5 µg/lb; horse 1) and 10 µg/kg (4.5 µg/lb; horses 2 and 3) of the compounded clenbuterol. In the United States, clenbuterol was approved by the FDA in 1998 for administration by mouth to horses for the treatment of respiratory disease. It is only available as a syrup (clenbuterol hydrochloride; 72.5 µg/mL) from a single manufacturer with no generic products available. The recommended maximum dose is 3.2 µg/kg (1.5 µg/lb). The serum concentration of clenbuterol detected in the first horse at admission was approximately 25 times as high as that expected for a horse given clenbuterol within the labeled dose range, on the basis of a 24-hour withdrawal time. The 3 horses in the present report were administered an illegal form of liquid clenbuterol by mouth from an unknown source by local animal care personnel. The illegal substance was obtained and administered to the horses without a prescription, with no apparent medical need or indication, and was therefore administered with no input or advice from a licensed veterinarian. The clenbuterol was administered from a poorly labeled container according to oral instructions. After the horses became sick, the incident was reported to the Louisiana State Veterinarian’s office, and an investigation involving the FDA and other officials was performed. News reports8,11 were disseminated statewide and nationwide warning equine caretakers and veterinarians of the presence of the illegal formulation of clenbuterol and the potential for harm.

In the United States, AMDUCA allows veterinarians to prescribe extralabel uses of certain animal and human drugs for animals under certain conditions. The use of compounded medications is considered extralabel use; therefore, the use of any compounded medication must meet all requirements of AMDUCA.12 The key requirement is the presence of a valid veterinarian-client-patient relationship. For legal use of a compounded medication, there are a number of specific additional requirements (notably, the lack of an approved animal drug that is labeled for the indicated use or that contains the same active ingredient in the required dosage form and concentration). Clearly, for the horses in the present report, none of these requirements were met. In fact, although the first horse was previously prescribed the legally available clenbuterol formulation, it subsequently received the compounded item instead, which resulted in severe illness and death. Administration of an essentially unknown substance by lay personnel resulted in the critical illness of 3 horses and death of 2 in the present report. It is believed that at least 10 additional horses from this particular racetrack and another in an adjoining state had similar adverse reactions with this same formulation of clenbuterol. Nonetheless, there was no criminal investigation by the police department or the FDA in response to the incident in the present report.

Documentation of high tissue concentrations of clenbuterol in the first and third patients in the present report may explain the prolonged clinical signs. In horse 1, serum concentration at 24 hours was 5.45 ng/mL; clenbuterol was detected in the liver at a concentration of 376.89 ng/mL and in the kidney at a concentration of 202.24 ng/mL. In horse 3, serum concentration at 114 hours was 1.03 ng/mL; clenbuterol was detected in the liver at a concentration of 6.79 ng/mL and in the kidney at a concentration of 1.70 ng/mL. Tissue clearance of clenbuterol is often prolonged relative to serum clearance, and prolonged detection of clenbuterol has been reported in the liver, kidneys, eye fluids, lungs, heart, and spleen when tissue distribution in clinically normal horses was evaluated. Because clenbuterol is metabolized in the liver and excreted in the urine, the liver and kidneys frequently contain concentrations of clenbuterol several times as high as that of serum.8,13,14 Although the clinical signs of clenbuterol toxicosis in the horses in the present report were very similar to many of the symptoms reported8,7,13,14 in humans, some of the clinicopathologic abnormalities appeared to be unique. In people, hypokalemia, hyperglycemia, hypomagnesemia, and neutrophilic leukocytosis are frequently reported.6,7,13,14 Hypokalemia in all 3 horses

---

[References are not explicitly listed in the provided text.]
in this report was mild to absent. Serum magnesium concentrations were not measured in these horses, but supplemental magnesium was provided on the basis of reports of hypomagnesemia in human patients with clenbuterol overdose. Immature (hand) neutrophils were detected in both nonsurviving horses, but only horse 1 had absolute neutrophilia at admission.

The predominant alteration in the serum biochemical profile of all 3 horses in the present report was severe hyperglycemia. Hyperglycemia results from induction of glycogenolysis by hepatic $\beta_2$-adrenoreceptors. We speculate that hyperglycemia may be compounded by prolonged exposure of hepatic tissues to clenbuterol; the drug is metabolized in the liver, and hepatic concentrations greatly exceed serum concentrations for several days. In contrast to human patients, hyperglycemia in the horses in the present report did not resolve spontaneously, and repeated administration of insulin was required to achieve normoglycemia. Severe hypoglycemia and hypochloremia have not been reported in humans, but both abnormalities were noted in both the horses in the present report that did not survive.

The adverse effects of clenbuterol may be broadly considered to arise from excessive adrenergic stimulation. Clenbuterol is a moderately selective $\beta_2$-adrenoreceptor agonist, but at higher doses, all classes of $\beta$-adrenoreceptors are activated. $\beta_2$-Adrenoreceptors are present in equine skeletal and cardiac myocytes, hepatocytes, nervous tissue, respiratory smooth muscle, vascular smooth muscle, uterus, and ileum. In the vasculature, therapeutic doses of clenbuterol initially produce a decrease in blood pressure, but this is counteracted within 2 minutes after administration by a reflex increase in heart rate and pulmonary arterial pressure. The higher doses of clenbuterol administered to the patients in the present report may have contributed to the profound hypotension and alterations in perfusion seen in the 2 more severely affected horses, possibly contributing to the development of laminitis in the third patient and complicating treatment of rhabdomyolysis in the first patient. $\beta_2$-Adrenoreceptors in the myocardium may be stimulated directly by clenbuterol or secondarily by norepinephrine released from presynaptic sympathetic neurons responding to $\beta_2$-adrenoreceptor activation. In both skeletal and cardiac muscle, however, direct toxicity is mediated via pathways downstream of the $\beta_2$-adrenoreceptor. In rats, a single administration of clenbuterol ≥ 10 µg/kg produces skeletal muscle necrosis, and doses ≥ 100 µg/kg induce cardiac necrosis. In the heart, this effect is most pronounced in the left ventricle. With repeated administration ≤ 10 µg/kg in rats, clenbuterol appears to induce muscle hypertrophy without adverse effects; the attenuation of myotoxic effects over time is thought to be related to downregulation of adrenoreceptors. Skeletal and cardiac muscle injury was evident in both nonsurviving horses in the present report. The dose of clenbuterol administered to the third patient was well below the dose that has been reported to induce cardiac necrosis in rats. Clenbuterol also activates $\beta_1$- (atypical)-adrenoreceptors, which are purportedly responsible for the lipolytic effects of clenbuterol, and which are relatively insensitive to blockade by the majority of $\beta$-adrenergic receptor antagonists, including propranolol. In horses, $\beta_1$-adrenoreceptors have been identified in vascular smooth muscle, adipocytes, liver, and the ileum. Activation of these receptors has been suggested to contribute to the poor response to $\beta$-adrenoreceptor blocker treatment in some affected horses.

A variety of targeted and symptomatic treatments have been used in human patients after accidental or intentional clenbuterol overdose, including $\beta$-adrenoreceptor blockers, antiemetics, potassium chloride, and anticonvulsants such as diazepam. The $\beta$-adrenoreceptor blockers, including propranolol, are the most pharmacologically direct means of counteracting $\beta$-adrenergic receptor stimulation. Together with potassium chloride administered IV, they are considered the treatment of choice for acute clenbuterol exposure in human medicine. In contrast to human patients, similarly, in the patients in the present report, repeated administration of propranolol was necessary and may have been a result of accumulation of clenbuterol in tissues or contributions from refractory $\beta_2$-adrenoreceptor activity. Although propranolol was effective in reducing the heart rate in all horses in this report, neither propranolol, any sedative agent, nor any of the analgesics administered were effective at reducing anxiety and muscle tremors. Provision of analgesia via a constant rate infusion of ketamine in conscious horses has been previously described. Administration of ketamine by use of this protocol was attempted for the third patient in the present report following the onset of laminitis. Although no adverse effects on mentation were noted, the desired analgesic effects were also not achieved for this horse. Its overall condition continued to deteriorate, and it did not survive.

a. Ventipulmin Syrup, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
b. Endosyrum, IMMVAC Inc, Columbia, Mo.
d. Guaifenesin (in 3% dextrose) for IV injection, 50 mg/mL, WedgeWood Pharmacy, Swedesboro, NJ.
e. Duragesic 100 µg/h, Ortho-McNeil-Janssen Pharmaceuticals Inc, Raritan, NJ.
g. Flunixin meglumine, Butler Animal Health Supply, Dublin, Ohio.
h. Pentoxifylline for IV injection, 4 g, HDM Pharmacy LLC, Lexington, Ky.
i. BioSponge, Platinum Performance, Buellton, Calif.

References