Severe phenylephrine-associated hemorrhage in five aged horses

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EQUINE

Case Description—5 aged (≥ 17 years old) horses developed life-threatening internal hemorrhage following IV administration of phenylephrine at 3 hospitals.

Clinical Findings—All 5 horses developed severe hemothorax, hemoabdomen, or both within minutes to hours following administration of phenylephrine.

Treatment and Outcome—Four of 5 horses died of hemorrhagic shock, and 1 horse survived with a blood transfusion. The exact source of hemorrhage was identified in only 1 horse. Medical records of all horses with nephrosplenic entrapment of the large colon and treated with phenylephrine at the University of Florida Veterinary Medical Center between 2000 and 2008 (n = 74) were reviewed. Three of these 74 (4%) horses developed fatal hemorrhage (horses 1 through 3 of this report). The risk of developing phenylephrine-associated hemorrhage was 64 times as high (95% confidence interval, 3.7 to 1,116) in horses ≥ 15 years old than in horses < 15 years old.

Clinical Relevance—The potential risks versus benefits of phenylephrine administration should be evaluated carefully, especially in old horses. (*J Am Vet Med Assoc* 2010;237:830–834)

A 17-year-old 507-kg (1,115-lb) American Paint Horse gelding (horse 1) was examined at the University of Florida Veterinary Medical Center with a 12-hour history of moderate signs of colic, including anorexia, pawing, and intermittent rolling. Treatments prior to hospital admission included administration of flunixin meglumine (1 mg/kg [0.45 mg/lb], IV, once), xylazine (0.4 mg/kg [0.18 mg/lb], IV, once), butorphanol (0.01 mg/kg [0.005 mg/lb], IV, once), and mineral oil (1 gallon via nasogastric tube, once).

On physical examination, the horse had a rectal temperature of 38.1°C (100.5°F), heart rate of 56 beats/min, and respiratory rate of 30 breaths/min. The horse was in good body condition (body condition score, 6/9) and was estimated to be 5% dehydrated with a slightly prolonged capillary refill time. Nasogastric intubation yielded no net reflux. On abdominal palpation per rectum, a medially displaced spleen with the large colon within the nephrosplenic space was detected. Findings on thoracic and abdominal ultrasonography were unremarkable except that the left kidney could not be imaged. The PCV and plasma total protein concentration were 28% and 7.3 g/dL, respectively. Venous blood gas tensions, blood lactate concentration, CBC, and findings on plasma biochemical analysis were all within reference limits. A diagnosis of left dorsal displacement of the large colon with nephrosplenic entrapment was made.

After IV placement of a catheter in the jugular vein, 30 mg of phenylephrine[a] diluted in 60 mL of saline (0.9% NaCl) solution was administered over 15 minutes. Immediately after the infusion, a brief self-limiting episode of cough, epistaxis, and hemoptysis was observed. Findings on upper airway endoscopy revealed that the mild hemorrhage had originated from the lungs. Prothrombin time, activated partial thromboplastin time, and concentration of fibrin split products were determined to be within reference limits. The horse was jogged for 20 minutes. Findings on abdominal palpation per rectum after jogging were inconclusive. At the time, the horse appeared comfortable and had a heart rate of 48 beats/min. The horse was placed under observation with hourly recording of heart rate and respiratory rate; fluid therapy with a replacement crystalloid solution[b] was initiated at a rate of 1.5 L/h. Approximately 6 hours following phenylephrine administration, the horse had a heart rate of 100 beats/min and white mucous membranes. On abdominal ultrasonography, a large volume of free echogenic fluid swirling within the pleural and abdominal cavities was observed. Major and minor crossmatch testing of blood was initiated in preparation for a blood transfusion, and the rate of IV administration of fluid was increased to 5 L/h. However, the horse died prior to blood transfusion.

Large volumes of blood within the pleural space (20 L), peritoneal cavity (20 L), and pericardial sac (1.5 L) were found on necropsy examination. In addition, the liver was diffusely firm with an accentuated lobular pattern and dark tan areas up to 3 mm in diameter. There were areas of hemorrhage within the small intestinal mesentery. Findings on histologic examination of liver tissue revealed a mild multifocal necrotizing hepatitis with mineralization. The lesions in the liver were believed to be incidental. No definitive cause could be found for the massive internal hemorrhage.

A 17-year-old Thoroughbred mare (horse 2) was examined for acute onset of colic. The mare was part of the University of Florida teaching herd and was ob-

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served to be recumbent and rolling. Physical examination was unremarkable in terms of vital signs, mucous membrane color, capillary refill time, and findings on thoracic and abdominal auscultation. On abdominal palpation per rectum, the presence of large colon within the nephrosplenic space and ventromedial displacement of the spleen were detected. The left kidney could not be imaged during abdominal ultrasonography. The amount of peritoneal fluid detected during ultrasonography was considered normal. After IV placement of a catheter in the jugular vein, phenylephrine (10 mg in 500 mL of saline solution) was administered over 15 minutes. The horse was lunged for approximately 10 minutes before it became weak and collapsed. The horse's condition continued to deteriorate over a period of approximately 20 minutes, at which time euthanasia was performed via IV administration of pentobarbital and phenytoin sodium.[c] Severe hemoabdomen caused by a rupture of a middle uterine artery with hemorrhage dissecting through the broad ligament was found on necropsy examination. The mare had not been bred during the 5 years she was part of the teaching herd. The mare's prior foaling history was unknown.

A 23-year-old 515-kg (1,133-lb) Thoroughbred gelding (horse 3) was examined at the University of Florida Veterinary Medical Center for colic. Treatments prior to hospital admission included administration of flunixin meglumine (1 mg/kg, IV, once), xylazine (0.25 mg/kg [0.11 mg/lb], IV, twice), and replacement crystalloid fluids (5 L, IV).[b] On physical examination, the horse was quiet, alert, and responsive with a rectal temperature of 37.9°C (100.3°F), heart rate of 44 beats/min, and respiratory rate of 12 breaths/min. The horse was in good body condition (body condition score, 5/9). The horse appeared to be adequately hydrated with pink mucous membranes and a capillary refill time of 1 second. Nasogastric intubation yielded no net reflux. Gastrointestinal borborygmi were decreased on the left side of the abdomen. Left dorsal displacement of the large colon into the nephrosplenic space with mild gas distention was detected on abdominal palpation per rectum. Findings on thoracic and abdominal ultrasonography were unremarkable except that the left kidney could not be imaged. Venous blood gas variables, blood lactate concentration, CBC, and findings on plasma biochemical analysis were all within reference limits. A diagnosis of left dorsal displacement of the large colon with nephrosplenic entrapment was made. After IV placement of a catheter in the jugular vein and administration of 5 L of a replacement crystalloid solution,[b] 20 mg of phenylephrine was diluted in 500 mL of saline solution and administered over 15 minutes. Immediately after administration of the full dose of phenylephrine, a small amount of blood was seen dripping from the left nostril. A few minutes later, the horse began coughing and expelled blood from the mouth and both nostrils. The epistaxis and hemoptysis ceased shortly thereafter. Approximately 10 minutes later, the horse became weak and reluctant to move. The horse was tachycardic with a heart rate of 80 beats/min, and mucous membranes were pale with a capillary refill time of 3 seconds. Indirect arterial pressure measurement via a tail cuff revealed a mean arterial pressure of 121 mm Hg. Treatments with acepromazine (0.04 mg/kg, [0.018 mg/lb], IV, once), intranasal oxygen insufflation (10 L/min), and aminocaproic acid (70 mg/kg [32 mg/lb], in 1 L of lactated Ringer's solution administered over 30 minutes) were initiated. After approximately 15 minutes, the mean arterial pressure had decreased to 89 mm Hg. A large amount of free echogenic fluid swirling within the pleural cavity, consistent with hemothorax, was observed on thoracic ultrasonography. Arterial lactate concentration was markedly high at 9.5 mmol/L (reference range, 0.3 to 1.7 mmol/L). The horse collapsed during preparation for thoracocentesis and autologous transfusion. The horse was euthanatized via IV administration of pentobarbital and phenytoin sodium[c]; the owner did not authorize a necropsy.

A 21-year-old 475-kg (1,045-lb) Thoroughbred gelding (horse 4) was examined at the University of Georgia Large Animal Teaching Hospital for evaluation of mild colic of 3 days' duration and 1 episode of fever (rectal temperature, 40.0°C [104°F]). One of 2 other horses on the farm had been evaluated previously at the University of Georgia and had a diagnosis of primary peritonitis of unknown etiology.

At the time of hospital admission, the horse appeared mildly uncomfortable. Its heart rate was 48 beats/min, respiratory rate was 24 breaths/min, and rectal temperature was 37.2°C (99°F). Nasogastric intubation yielded no net reflux. Findings on abdominal palpation per rectum were unremarkable. Findings on abdominal ultrasonography revealed a subjectively large spleen, which could be seen on the ventral portion of the abdomen approximately 10 cm to the right of midline. In addition, a homogeneous, hyperechoic, spherical structure, measuring approximately 8 to 9 cm in diameter, was seen in the left caudodorsal portion of the abdomen in the area of the paralumbar fossa. Findings on CBC determination and serum biochemical analysis were unremarkable.

A dose of phenylephrine (10 mg in 500 mL of saline solution) was administered IV over 10 minutes in an attempt to induce splenic contraction and facilitate abdominocentesis. Peritoneal fluid analysis revealed a high total nucleated cell count (22,400 cells/μL; reference limit, < 5,000 cells/μL) and total protein concentration (3.1 g/dL; reference limit, < 2.5 g/dL). Cytologic evaluation of peritoneal fluid revealed 93% nondegenerate neutrophils, 2% lymphocytes, and 5% large mononuclear cells. No infectious agents or neoplastic cells were seen. Results of aerobic and anaerobic bacteriologic cultures of peritoneal fluid were subsequently negative for bacterial growth.

A diagnosis of a low-grade peritonitis of unknown etiology was made. Exploratory celiotomy was declined by the owner. Treatment with flunixin meglumine (1 mg/kg, IV, q 12 h), potassium penicillin (22,000 U/kg [10,000 U/lb], IV, q 6 h), and gentamicin (6.6 mg/kg [3.0 mg/lb], IV, q 24 h) was initiated. A CBC was repeated 3 days following admission and revealed that the horse had hyperfibrinogenemia (600 mg/dL; reference range, 200 to 500 mg/dL) with a mild neutrophilic left shift. Ultrasound-guided biopsy specimens of the spleen were obtained for histologic examination and submitted for bacteriologic and fungal cultures. Prior

to biopsy, results of a coagulation profile including a prothrombin time, activated partial thromboplastin time, and thrombin time were within reference range. Findings on histologic examination of the spleen revealed congestion and hemosiderin deposition without evidence of infectious organisms or neoplasia. Abdominal palpation per rectum was repeated, and a firm, lobulated mobile abdominal mass was identified. The following day, however, the abdominal mass was not identified on abdominal palpation per rectum or abdominal ultrasonography; this suggested that the mass was mobile within the abdomen.

After 6 days of treatment with potassium penicillin and gentamicin, antimicrobial treatment was changed to chloramphenicol (50 mg/kg [22.7 mg/lb], PO, q 8 h) for the treatment of a presumptive abdominal abscess. Despite antimicrobial treatment, the horse continued to have intermittent episodes of pyrexia. On day 9 after admission, a CBC was repeated and revealed an increase in the plasma fibrinogen concentration to 700 mg/dL. A second abdominocentesis did not yield peritoneal fluid. A subjectively large spleen occupying the cranioventral portion of the abdomen was observed on abdominal ultrasonography. Phenylephrine (20 mg in 60 mL of saline solution) was administered over 10 minutes via an indwelling IV catheter to facilitate abdominocentesis. The horse's heart rate was monitored for the duration of administration and remained between 32 and 36 beats/min. Peritoneal fluid was collected, and analysis revealed an improved total nucleated cell count (8,900 cells/μL) with a persistently high total protein concentration (6.5 g/dL).

Approximately 5 minutes following the end of phenylephrine administration, the horse developed signs of abdominal discomfort such as pawing and flank watching. A few minutes later, the horse became acutely shaky, sweaty, and agitated. On cardiac auscultation, a tachyarrhythmia (heart rate, 180 to 200 beats/min) was detected. The horse had pale mucous membranes, and peripheral pulses were not palpable. The horse collapsed and died within 10 minutes despite intranasal oxygen administration.

On necropsy examination, a large amount of blood was present in the pleural space and the cause of death was considered to be hemothorax. Diffuse subserosal hemorrhages were observed in the tunica media of the esophagus. In addition, multiple myofibers of the muscularis in the area were hypertrophied. Large amounts of hemorrhage admixed with fibrin and degenerate neutrophils extended from the periesophageal tissue into adjacent adipose tissue. Within the adjacent adipose tissue were multiple arteries with prominent internal elastic membranes. The mass in the abdomen was a necrotic lipoma with associated serosal hemorrhage and inflammation.

A 32-year-old 498-kg (1,095-lb) Thoroughbred gelding (horse 5) was referred to Byron Reid and Associates, Loxahatchee, Fla, for an episode of colic of approximately 4 hours' duration. A previous exploratory laparotomy to correct a nephrosplenic entrapment of the large colon was performed approximately 3 years prior to admission. Treatment administered by the referring veterinarian consisted of flunixin meglumine (1 mg/kg, IV, once) and xylazine (0.2 mg/kg [0.09 mg/lb], IV, once).

On physical examination, the horse was bright, alert, and responsive and was clinically normal in terms of vital signs. The horse was slightly underweight (body condition score, 4/9) and appeared to be adequately hydrated with pink and moist mucous membranes and a capillary refill time of 1 to 2 seconds. A gas-distended large colon in the left dorsal aspect of the abdomen was detected on abdominal palpation per rectum. Nasogastric intubation yielded no reflux. Findings on abdominal ultrasonography were unremarkable except that the left kidney could not be imaged. Results of serum biochemical analysis and CBC were within reference limits. Initial treatment consisted of IV administration of a balanced electrolyte solution[b] and the withholding of food. The horse continued to have mild signs of abdominal discomfort in the form of circling the stall and intermittent pawing.

On day 2, dorsal displacement of the left colon within the nephrosplenic space was detected on abdominal palpation per rectum. The left kidney or the dorsal half of the spleen was not evident on abdominal ultrasonography. A diagnosis of left displacement of the large colon with nephrosplenic ligament entrapment was made. On day 3, a CBC was repeated and revealed a PCV of 38% and plasma total protein concentration of 7.2 g/dL. Findings on abdominal palpation per rectum and abdominal ultrasonography remained unchanged. The amount of peritoneal fluid imaged during abdominal ultrasonography was considered normal. A constant rate infusion of phenylephrine was initiated (20 mg in 500 mL of saline solution at a rate of approx 1 mg/min). The horse's heart rate prior to the infusion was 64 beats/min. Approximately 20 minutes after initiation of the phenylephrine infusion, the horse had signs of abdominal discomfort in the form of lying down, rolling, and pawing. The infusion was stopped, but approximately 450 mL of the infusion had already been administered. The horse stood up quietly for approximately 10 minutes before collapsing. A bolus of a balanced electrolyte solution[b] was initiated, and the horse was administered flunixin meglumine (1 mg/kg, IV), dexamethasone (0.04 mg/kg, IV), and hypertonic saline solution (4 mL/kg [1.8 mL/lb], IV). The horse had signs of mild discomfort for the next several hours. Plasma total protein concentration and PCV measured approximately 5 hours after administration of phenylephrine were 4.0 g/dL and 19%, respectively. The horse's mucous membranes at this time were pale to white, and the heart rate was 96 beats/min. Abdominal ultrasonography was repeated; a large amount of echogenic free fluid swirling in the abdomen, consistent with hemoabdomen, was observed. The source of the hemorrhage was not identified. A blood transfusion with 8 L of fresh whole blood was administered.

On the morning of day 4, the PCV and plasma total protein concentration were 21% and 5.1 g/dL, respectively. Findings on abdominal palpation per rectum on day 9 revealed no clinically relevant abnormalities. A decreased amount of free fluid in the abdomen, compared with that observed previously, was found on abdominal ultrasonography. The horse was discharged on day 12 with a PCV of 32% and plasma total protein concentration of 6.9 g/dL.

The medical records of all horses admitted to the University of Florida Veterinary Medical Center between 2000 and 2008 with a diagnosis of nephrosplenic entrapment of the large colon were examined. Diagnosis was made by a combination of abdominal palpation per rectum and inability to image the left kidney during abdominal ultrasonography, or was made during exploratory laparotomy. Of 106 horses with a nephrosplenic entrapment of the large colon, 74 received phenylephrine and were either jogged, rolled, or a combination of these 2 nonsurgical treatments. The median age of these 74 horses was 6 years (range, 9 months to 24 years). The median dose of phenylephrine was 20 mg (range, 5 to 30 mg). Three of the 74 (4%) horses administered phenylephrine developed fatal hemorrhage (horses 1 through 3 of this report). The association between age or dose of phenylephrine and development of phenylephrine-associated hemorrhage was evaluated by use of logistic regression. There was no significant ($P = 0.824$) association between dose of phenylephrine and development of hemorrhage. Odds of phenylephrine-associated hemorrhage developing were 1.4 times as high (95% confidence interval, 1.1 to 1.8) with each additional year of age ($P = 0.012$). The best age cutoff for the development of phenylephrine-associated hemorrhage was assessed by use of receiver operating characteristic curve analysis.[1] The area under the receiver operating characteristic curve for the ability of age to predict development of phenylephrine-associated hemorrhage was 0.97 (95% confidence interval, 0.89% to 0.99%; $P < 0.001$). The ideal cutoff point was 15 years, resulting in a sensitivity of 100% and specificity of 95.3%. The risk of developing phenylephrine-associated hemorrhage was 64 times as high (95% confidence interval, 3.7 to 1,116) in horses ≥ 15 years old than in horses < 15 years old ($P = 0.004$). All statistical analyses were performed by use of a commercial software package.[d]

Discussion

Nephrosplenic entrapment of the large colon is a commonly diagnosed condition in horses. In 1 report,[2] 5.8% of horses admitted to an equine referral hospital for colic were diagnosed with nephrosplenic entrapment of the large colon. Results from the same study[2] found that 37% of large colon displacements were nephrosplenic entrapments. The prognosis for horses with nephrosplenic entrapments is typically good with survival rates ranging from 84% to 100%.[2–5] Treatment for this type of colic ranges from conservative medical treatment to exploratory surgery. Medical treatment often includes the use of phenylephrine, a vasoconstrictive agent, in combination with exercise or rolling the horse under general anesthesia. The rate of successful resolution of nephrosplenic entrapments following administration of phenylephrine ranges between 56% and 92%.[4,5]

Phenylephrine acts on α_1-adrenergic receptors to cause systemic vasoconstriction and splenic contraction. Previously reported adverse effects of phenylephrine administration to horses are typically inconsequential and include bradycardia, hypertension, second-degree atrioventricular blocks, and premature ventricular contractions.[6,7] Rare complications of phenylephrine administration in humans include severe hypertension, pulmonary edema, and death.[8] To the authors' knowledge, hemothorax or hemoabdomen associated with phenylephrine administration has not been reported for humans or animals. However, administration of phenylephrine or other sympathomimetics contained in over-the-counter drugs has been associated with intracerebral and subarachnoid hemorrhage in people.[9,10]

The complications described in this report might have been initiated by vasoconstriction and secondary hypertension. In horse 3, indirect mean arterial blood pressure was measured shortly after administration of the drug and found to be markedly high. However, hypertension is a common and inevitable effect of IV administration of phenylephrine[6,11] while severe hemorrhage as reported here is rare. Cardiovascular disease, decreased vessel compliance, and atherosclerosis are well-recognized complications associated with aging in humans.[12,13] The possibility of reduced vessel compliance and altered vessel elasticity associated with aging in horses is of particular interest given the significant association of phenylephrine-associated hemorrhage with age in the present report and the fact that all affected horses were > 15 years of age. To the authors' knowledge, the effect of aging on the overall vasculature of horses has not been described. However, aging in mares results in endometrial arterial and venous angiosclerotic changes characterized by perivascular and intimate sclerosis.[14] Hyperplasia of intimal elastic fibers and thinning of the smooth muscle layers of uterine wall arteries also occur with aging in mares.[15]

There was confirmation of massive internal hemorrhage in the 3 horses submitted for necropsy examination, but a definitive source of the bleeding was only identified in 1 horse. It is plausible that a preexisting angiopathy or aneurism not discovered during necropsy might have been present. In horse 4, it was unclear whether the abnormal esophageal vasculature played a role in development of hemothorax. Activation of coagulation and altered laboratory coagulation parameters can frequently be found in horses with gastrointestinal disease.[16,17] Blood samples for laboratory testing aimed at diagnosing underlying clotting disorders such as hypo- or hypercoagulability, disseminated intravascular coagulation, and hyperfibrinolysis were submitted in 2 of 5 horses in the present report, and results were found to be within the reference range. Nevertheless, an underlying coagulopathy cannot be completely ruled out.

A mild and transient episode of epistaxis or hemoptysis was observed immediately after administration of phenylephrine in 2 horses in the present report. Both horses died later from hemorrhagic shock secondary to internal hemorrhage. This suggests that horses developing epistaxis or hemoptysis after administration of phenylephrine should be monitored closely for internal hemorrhage and that preparation for a blood transfusion (eg, cross-matching and preparation of a donor) should be initiated even if the amount of external blood loss appears inconsequential.

The rate of severe complications from IV administration of phenylephrine to horses is low. Nevertheless, phenylephrine-associated hemorrhage is possible and may result in death. This complication appears more

likely in old horses. The potential risks versus benefits of phenylephrine administration should be evaluated carefully, especially in old horses.

a. Baxter Healthcare Corp, Irvine, Calif.
b. Normosol R Abbott Animal Health, Abbott Park, Ill.
c. Beuthanasia D Special Intervet/Schering-Plough Animal Health, Millsboro, Del.
d. MedCalc for Windows, version 9.4.2.0, MedCalc Software, Mariakerke, Belgium.

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