Treating Cantharidin Toxicosis

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At a Glance

Series Editor

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Cantharidin toxicosis in horses is most common in the southwestern United States and is associated with the ingestion of alfalfa hay contaminated with blister beetles. While 67 species of blister beetles have been identified in Oklahoma alone, the most common species associated with toxicosis in horses are the three-striped blister beetles (*Epicauta temexa* and *Epicauta occidentalis*)[1,2] (**FIGURE 1**). Because the geographic range of blister beetles is extensive and importation of alfalfa hay harvested from high-risk regions is possible, equine veterinarians should be familiar with the diagnosis and treatment of cantharidin toxicosis regardless of practice location. Gas chromatography and mass spectrometry of urine or gastric contents can be used to confirm the diagnosis.[1]

Differential Diagnosis

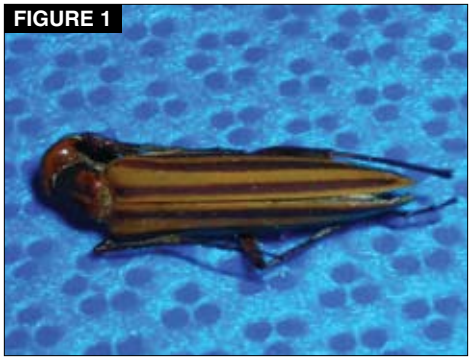
The clinical presentation of cantharidin toxicosis can vary greatly but is generally a consequence of the toxin's (1) irritation of the gastrointestinal (GI) and renal systems and (2) action at specific molecular receptors (**BOX 1**). Patient variation and the dose of toxin ingested influence the clinical presentation. Multiple horses on the farm may be affected. Monensin, arsenic, and blue-green algae toxicoses may also cause sudden death in multiple horses and are plausible diagnostic possibilities.[3]

When clinical signs of colic predominate, the differential diagnosis will likely be influenced by the horse's severity of pain and the presence or absence of other clinical signs, including fever and diarrhea. Because fever is very common in equine patients with cantharidin toxicosis, differentials such as colitis, proximal enteritis, and peritonitis are important to consider. Although general causes of colic are extensive, clinicians should primarily focus on those representative of all the clinical signs.

Horses with minimal toxin ingestion may present with mild lethargy and anorexia, while ingestion of higher doses of cantharidin can culminate in signs of hypovolemic shock and in death. Other conditions to consider in horses displaying signs of endotoxic shock include GI rupture, colitis, proximal enteritis, NSAID toxicosis, and prolonged strangulating obstructions. Occasionally, cantharidin-intoxicated horses exhibit extreme pain that is difficult to control with analgesics and mimics a surgical intestinal lesion.

Early in the clinical course of sublethal toxicosis, horses often display ptyalism and submerge their muzzles in their water buckets to agitate the water. Frequently, this "water playing" behavior is violent, which complicates monitoring water consumption. Oral ulcerations may be present

FIGURE 1



Three-striped blister beetle.

Common Clinical Signs Associated With Cantharidin Toxicosis

BOX 1

Physical examination findings

- Tachycardia
- Colic
- Fever
- Dysuria
- Lethargy and anorexia in mild cases
- Hypovolemic shock or death in severe cases
- Ptyalism and playing in water bucket
- Diarrhea

Laboratory abnormalities

- Hyposthenuria (urine specific gravity: 1.004–1.007)
- Microscopic hematuria
- Hypocalcemia
- Hyperglycemia
- Hypomagnesemia

CriticalPoint

Pyrexia, dysuria, and colic are common clinical signs of cantharidin toxicosis. However, some horses may present with pyrexia, lethargy, and anorexia without signs of abdominal pain.

but, in my experience, are uncommon. Some horses display bruxism, which may be due to oral or, more likely, gastric pain because squamous epithelial ulceration is common.

During renal excretion, cantharidin induces urinary tract irritation and hemorrhage, resulting in signs of dysuria. Clinical signs can vary from pollakiuria to polyuria. Frequently, the urine is clear and dilute before fluid therapy is instituted. Hyposthenuria (urine specific gravity: 1.004 to 1.007) associated with cantharidin toxicosis is common, regardless of hydration status; in equine patients with renal failure, an isosthenuric urine specific gravity (1.008 to 1.014) is common. Hyposthenuria associated with cantharidin toxicosis is most likely due to inhibitory action of the toxin on protein phosphatase 2A receptors in the renal cortical collecting duct. In experimental rodent models, phosphatase 2A inhibition interfered with the action of vasopressin and thus water and sodium reabsorption in the kidneys.[4] Microscopic hematuria is common due to the irritant effects of cantharidin on the urinary epithelium. Geldings and stallions may exhibit paraphimosis or priapism.

Clinical Pathology

The most consistent laboratory finding in equine patients with cantharidin toxicosis is hypocalcemia; however, the absence of it does not preclude this diagnosis (**BOX 1**). Concurrent clinical signs may include muscle fasciculations, synchronous diaphragmatic flutter, abnormal facial expression, weakness, ataxia, or a stilted gait. Other common clinicopathologic findings include hyperglycemia, hypomagnesemia, or an increased serum creatine kinase level. Rarely, cantharidin toxicosis may present with clinical and laboratory evidence of significant myopathy (creatine kinase: >200,000 IU); other causes of rhabdomyolysis should be considered in these cases. Myocardial necrosis has been documented at necropsy in some horses with fatal cantharidin toxicosis.[5] While biochemical evidence of myocardial injury is common in horses with cantharidin toxicosis, myocardial dysfunction of clinical significance appears to be rare.[6]

Characteristic abnormalities on urinalysis include microscopic hematuria and hyposthenuria. Cytology of an abdominocentesis sample may reveal an increased total protein level and leukocyte count.[7] Neutrophilic leukocytosis is common, although equine patients occasionally display neutropenia and/or left shift as well as lymphopenia. Although metabolic acidosis can occur, mixed acid–base responses are more common.

Treatment

General treatment goals include elimination of toxin exposure, reduction of toxin absorption, pain management, correction of fluid and electrolyte deficits, and GI mucosal protection. In addition, prophylactic therapy for potential complications is often warranted.

Oral Adsorbents

Activated charcoal (1 to 3 g/kg) can be administered via nasogastric tube to promote GI toxin elimination. Depending on the estimated time of toxin ingestion, an oral adsorbent may be administered every 12 hours for two or three treatments. Cantharidin is lipid soluble; thus, dietary sources of oil could increase cantharidin absorption, potentiating toxicosis. Therefore, grain sources and nutritional supplements containing fat should be discontinued. Because mineral oil is poorly absorbed, some have suggested it may be useful to potentiate toxin removal.[7] However, studies at my laboratory comparing the cantharidin adsorptive activity of mineral oil, activated charcoal, and di-

tri-octahedral smectite suggest mineral oil is a poor choice for toxin adsorption when activated charcoal is available. If the clinician decides to administer mineral oil with other adsorbents, they should not be administered concurrently in order to avoid potential interaction. While activated charcoal was most effective at cantharidin adsorption in my laboratory's in vitro studies, di-tri-octahedral smectite is a valid alternative if activated charcoal is not available.

Pain Management

Analgesic options to treat abdominal pain associated with toxicosis include NSAIDs, α_2-agonists, and narcotics. Pain control may be achieved with flunixin meglumine (1.1 mg/kg IV), but additional analgesics may be necessary. The dose and frequency of NSAIDs used should be minimized because GI mucosal lesions and hypovolemia are common with cantharidin toxicosis. Xylazine (0.3 to 0.5 mg/kg IV) and detomidine (0.01 to 0.02 mg/kg IV) are also useful for short-term analgesia. Clinically, I find butorphanol to be more useful than α_2-agonists for managing severe or recurrent pain associated with cantharidin toxicosis. A loading dose of 20 µg/kg IV followed by a constant-rate infusion of 13 µg/kg/hr IV diluted in lactated Ringer's solution is commonly used for managing affected equine patients in my hospital. While the effects of cantharidin on nociception in horses are unknown, it was recently demonstrated that cantharidin interferes with the analgesic properties of α_2-agonists in rats but has no effect on narcotic κ-agonists such as butorphanol.[8]

Fluid Therapy

Fluid therapy is indicated to correct hypovolemia as well as electrolyte and acid–base derangements. In addition, promotion of diuresis may increase renal toxin excretion. Appropriate fluid administration rates are initially dictated by the severity of hypovolemia and shock, if present. Monitoring the response to fluid therapy can be particularly challenging in these patients. Preexisting hyposthenuria and polyuria negate the usefulness of monitoring urine output and urine specific gravity to guide fluid administration rates. Furthermore, ptyalism and water-playing behavior can alter interpretation of mucous membrane hydration. Therefore, the clinician should critically evaluate other clinical signs of tissue perfusion (e.g., mentation, heart rate, pulse quality, distal limb temperature, blood pressure, blood test results such as blood gas values) when estimating fluid administration rates. In severely affected equine patients, large-bore (10- to 12-gauge) catheters allow more rapid delivery of balanced electrolytes. Because ionized and total serum calcium concentrations are often low and blood pH can influence ionization, these parameters should be assessed.

Frequently, the severity of hypocalcemia in these patients requires administration of large quantities of intravenous calcium for 2 to 5 days. While the calcium deficit can be estimated mathematically, ongoing losses are common in severely affected equine patients, so it may be more practical to supplement calcium at a moderate rate and reassess serum biochemistry. To avoid cardiac toxicity, it is safer to administer calcium diluted in non–bicarbonate-containing isotonic fluids through a separate catheter at a slower rate than fluids for shock support. Depending on the severity of hypocalcemia, I typically add 250 to 500 mL of 23% calcium borogluconate per 5-L bag of isotonic fluids administered at a maintenance rate in managing severe cantharidin toxicosis. To maintain appropriate therapy, it is often necessary to repeat serum chemistry analysis two or three times daily.

Because many of these patients are also hypomagnesemic, polyionic-concentrated solutions containing calcium and magnesium are also used. However, when serum chemistry reveals significant hypomagnesemia, supplementation with concentrated magnesium products is usually necessary. It is important to restore a normal serum magnesium concentration because parathyroid hormone secretion in response to hypocalcemia may be impeded by hypomagnesemia. I recently documented inappropriately low parathyroid hormone concentrations in a number of hypocalcemic horses with cantharidin toxicosis. In vitro studies using bovine parathyroid cell systems indicate that pharmacologic inhibition of protein phosphatase receptors impedes parathyroid hormone secretion.[9]

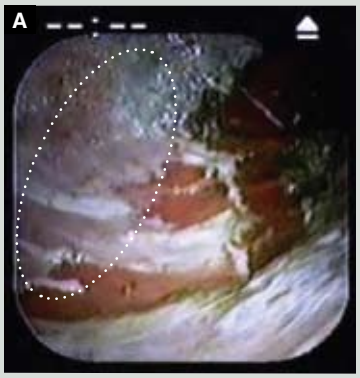
Gastrointestinal Protectants

Toxic effects of cantharidin on GI mucosa include gastric squamous epithelial ulceration, glandular mucosal irritation, and small intestinal

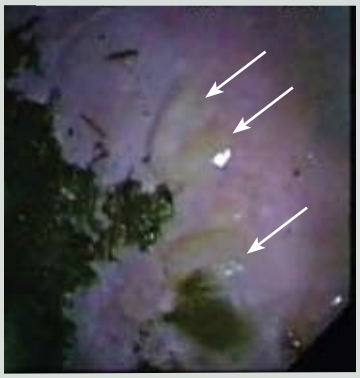
CriticalPoint

The common clinicopathologic findings of cantharidin toxicosis are hypocalcemia, hypomagnesemia, an increased creatine kinase level, and hyposthenuria.

FIGURE 2 **Gastroscopy images.**



Sheets of nonadherent desquamated epithelium adjacent to superficial ulcerations (*ellipse*) in the nonglandular stomach.



Raised, fluid-filled squamous epithelial "blisters" (*arrows*) in the nonglandular stomach.

and colonic inflammation.[5] Gastroscopic findings likely depend on the time elapsed since toxin ingestion. Evidence of recent exposure includes fluid-filled squamous epithelial blisters and pale sheets of nonadherent desquamated squamous epithelium in the nonglandular portion of the stomach (**FIGURE 2**). After complete desquamation, coalescing bands of superficial ulceration are common in the nonglandular stomach above the margo plicatus concurrent with glandular mucosal hyperemia. I often administer sucralfate (22 mg/kg PO q6h) for GI protection. In addition, omeprazole dosed at 4 mg/kg PO q24h may be administered to reduce gastric acidity and promote healing of gastric ulcers. Long-term (>7 to 14 days) omeprazole therapy may not be indicated because clinical experience indicates that resolution of squamous epithelial superficial erosions is fairly rapid.

CriticalPoint

The treatment goals for cantharidin toxicosis are pain management, gastroprotection, correction of electrolyte and fluid imbalances, and prevention of further toxin absorption.

Goal-Specific Therapy

Endotoxemia

Considering the histologic severity of GI mucosal damage documented on postmortem examination, coupled with common clinical signs (i.e., mucous membrane congestion, tachycardia, tachypnea, other signs of circulatory shock) in equine patients with documented cantharidin toxicosis, endotoxemia is likely integrally involved in the pathophysiology. Therefore, rational therapy also addresses the systemic effects of endotoxin absorption. In addition to fluid resuscitation and administration of low doses of flunixin meglumine (0.25 mg/kg IV q8h), polymyxin B (6000 U/kg IV q8–12h) can be used for its endotoxin-binding properties during the initial treatment period (typically 1 to 3 days). When azotemia is present, the frequency of polymyxin B administration and the dose and frequency of NSAID administration should be minimized. While profound neutropenia is rarely associated with cantharidin toxicosis, systemic antimicrobial therapy is occasionally indicated in select cases with increased risk of secondary infection.

Laminitis

Acute laminitis is a significant complication in approximately 10% of cantharidin toxicosis cases in my hospital. Currently, there is a paucity of scientific data addressing prophylactic therapy for acute laminitis. In my hospital, deep sand bedding is commonly provided for equine patients at high risk for developing laminitis. Aspirin therapy (20 mg/kg PO every other day) aimed at altering platelet function to prevent vascular occlusion associated with acute laminitis is often administered. When equine patients that develop acute laminitis and dorsal capsular rotation (i.e., third-phalanx rotation without distal displacement; "sinking") are treated, biomechanical forces should be addressed by using corrective shoeing methods to control pain and stabilize the third phalanx. The most effective methods I use incorporate three basic principles: heel elevation, improved breakover, and viscoelastic weight support of the caudal sole and heel region. Analgesic options include several NSAIDs: phenylbutazone, flunixin meglumine, ketoprofen, and firocoxib. In addition, combination analgesic protocols using constant-rate infusions of intravenous lidocaine (2 mg/kg bolus followed by 50 µg/kg/min) and butorphanol have been successfully used in select cases to minimize NSAID doses.

Managing Pregnant Mares

While little is known regarding the transplacental absorption of cantharidin, therapy to maintain fetal viability is an important goal in pregnant mares. In rats, cantharidin inhibits steroidogenesis; thus, it is plausible that similar effects could alter progesterone synthesis in pregnant mares with cantharidin toxicosis.[10] In addition, the risk of concurrent endotoxemia is substantial. Because endotoxemia alone can lower endogenous progesterone production in

early pregnancy in mares, I recommend administering altrenogest (0.044 mg/kg PO q24h).[11]

Conclusion

With early recognition and appropriate aggressive therapy, clinical experience suggests that most equine patients with cantharidin toxicosis recover.

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