

ACVIM

Wrap Up

MICHELLE N. ANDERSON
AND ERICA LARSON

Say your horse has a fever of unknown origin and your veterinarian has exhausted his resources trying to pinpoint the cause. Or, maybe your horse is exhibiting neurologic signs and your vet is looking for a peer's input to aid in diagnosis and treatment.

At that point, your general equine practitioner might contact or refer to a veterinarian certified with the American College of Veterinary Internal Medicine (ACVIM). These specialists focus on internal systems and, quite literally, know animals inside as well as out. And, veterinary internal medicine specialists working with a variety of species gather at the ACVIM Forum each year to present research results, share successes and challenges, and learn from each other.

This year's forum, aptly titled "Elevate Your Knowledge," held in Seattle, Wash., offered a robust selection of equine-related internal medicine topics, ranging from respiratory problems to endocrine disorders. We at *The Horse* attended those lectures and sifted through research to bring you this year's ACVIM Forum highlights. Here's what you need to know.

Supplement Reduces Gastric Ulcer Recurrence

Owners who've had horses with gastric ulcers know firsthand how frustrating—and expensive—it is to manage this often chronic condition. And with an estimated 75% of horses suffering from gastric ulcers, it's no surprise that treatment and

prevention of the condition—which is common enough to have its own acronym, EGUS (equine gastric ulcer syndrome)—has become big business.

The array of products, supplements, ingredients, and botanicals touted as the next "big thing" in EGUS management, as well as anecdotal success stories found online, left Frank Andrews, DVM, MS, Dipl. ACVIM, and his research team at Louisiana State University's (LSU) School of Veterinary Medicine wondering about the validity of company and consumer claims.

"Many supplements are marketed on the Internet (for treatment and prevention of gastric ulcers in horses), including one I call 'faith,' but little is known about their effectiveness," Andrews said. "When horse owners feed these advertised antiulcer supplements they're literally 'going on faith,' because there's very little scientific information available on the efficacy of these products in horses."

The clinical success of the drug omeprazole (marketed as GastroGard) to treat gastric ulcers is well-documented in the equine veterinary world. Long-term EGUS management is a bit trickier, and gastric ulcer recurrence is common, Andrews noted.

The LSU study researchers examined the use of SmartGut Ultra in horses after the animals received omeprazole to treat nonglandular ulcers (the most common equine gastric ulcers, occurring in the upper part of the stomach). SmartGut Ultra, a supplement marketed by SmartPak Equine, contains sea buckthorn, pectin and lectin, glutamine, and aloe vera.

Andrews and his team performed a masked crossover study of two 42-day period on eight mature Thoroughbreds. The team divided the horses into two groups and sorted the animals by nonglandular ulcer lesion score and then by sex. One

The researchers supplemented eight stalled horses for 42 days.

CUX PHOTOGRAPHY/SHAWN HAMILTON

group of horses underwent SmartGut Ultra treatment during the first study period while the other group served as controls (no treatment); during the second study period the groups switched treatment protocols. All horses were stall-confined and subjected to alternating periods of feed-deprivation, both factors known to contribute to gastric ulcer development.

The researchers performed gastroscopy on the day before the study began and again on Days 14, 28, 35, and 42, and a blinded clinician scored each horse based on nonglandular lesion number (NGN, meaning quantity) and severity (NGS). They also measured gastric juice pH (low stomach pH is normal for horses but can be associated with ulcers, Andrews said).

Not surprisingly, he noted, average NGN and NGS scores decreased significantly in all horses after two weeks of omeprazole treatment.

Two weeks after the team discontinued omeprazole administration, average NGN scores did not increase significantly in the treated horses, whereas NGN scores increased significantly in untreated control horses, Andrews said.

By Day 35, after feed-deprivation, NGN scores increased in both groups, but NGN scores were significantly lower in the SmartGut Ultra-treated horses than in the untreated controls on the same day. However, SmartGut Ultra did not alter the normal acid pH of the stomach significantly.

Overall, SmartGut Ultra treatment resulted in fewer ulcers two weeks after discontinuing omeprazole treatment and resulted in lower gastric ulcer numbers after feed deprivation than in the untreated group, without altering gastric juice pH, Andrews explained.

The research team concluded that SmartGut Ultra supplementation might be an affordable alternative to help protect the nonglandular stomach from the rebound acid effects once omeprazole treatment is discontinued and for stall-confined horses undergoing intermittent or scheduled feedings.

Andrews also noted that this product isn't a substitute for omeprazole paste treatment for gastric ulcers but, rather, an aid in maintaining stomach health.

Inhaled Corticosteroids, Management Changes for Heavey Horses

Imagine horses with recurrent airway obstruction (RAO, or heaves) wearing

VITAMIN E FOR NEUROLOGIC DISORDERS

Carrie Finno, DVM, PhD, Dipl. ACVIM, a researcher in the University of Minnesota Equine Neuromuscular Diagnostic Laboratory, presented a review of vitamin E supplementation in horses with neurologic disorders.

Vitamin E is a biologic antioxidant believed to help horses maintain normal neuromuscular function, Finno explained. "Vitamin E ... is a complex nutrient consisting of eight closely related, fat-soluble, naturally occurring compounds that form two groups: tocopherols (saturated) and tocotrienols (unsaturated)," she said. "There are four individual isoforms— α , β , γ , and δ —within each group. The majority of the commercially available vitamin E supplements for horses contain natural or synthetic α -tocopherol, the most biologically active (or available) and researched isoform."

Many horses with vitamin E deficiencies show no outward ill effects, Finno said. A select few, however, develop signs of neuromuscular disease. Some of the disorders linked to vitamin E deficiencies include neuroaxonal dystrophy and equine degenerative myeloencephalopathy, vitamin E deficient myopathy, and equine motor neuron disease. While vitamin E deficiencies play a role in these issues, she said veterinarians must consider other factors during diagnosis: "The diagnosis of (these) neuromuscular disorders ... requires not only determination of vitamin E status, but also the appropriate clinical signs, supporting clinical pathology and/or muscle biopsy results, and elimination of other possible diseases."

Determining vitamin E status involves measuring serum α -tocopherol concentrations in order to confirm any underlying deficiency and monitor supplementation's efficacy, Finno said. Monitoring levels is important because although vitamin E doesn't accumulate in horses' bodies to the point of toxicity, some disorders—including coagulopathy (impaired blood clotting) and impaired bone mineralization and beta-carotene absorption—have been reported in horses with very high dietary vitamin E concentrations, Finno said. The current vitamin E recommendation for mature horses is 1 to 2 IU/kg (international units per kilogram) body weight per day, she said.

Owners supplementing their horses with vitamin E should select natural-source, water-dispersible forms because they are "five to six times more bioavailable (a greater amount is absorbed by and made available in the horse's body) than synthetic vitamin E," she said.

—Erica Larson, *TheHorse.com*/32115

Darth Vader-like masks and breathing in corticosteroids every day. That was essentially the scene at the Université de Montréal in Quebec, Canada, during a yearlong study in which Mathilde Leclerc, DVM, PhD, Dipl. ACVIM, and colleagues investigated the effect of inhaled corticosteroids (ICS) and limiting exposure to allergens in horses with RAO.

“Avoiding hay and barn dust leads to a better control of lung inflammation.”

DR. MATHILDE LECLERE

Recurrent airway obstruction is a chronic and debilitating equine condition formerly known as chronic obstructive pulmonary disease. It describes a

condition similar to asthma in humans in which the horse seemingly cannot "catch its breath."

For the study, the researchers employed 11 heaves-afflicted horses stabled and exposed to hay to induce RAO clinical signs, including coughing, increased respiratory effort, nasal discharge, and abdominal lift at the end of exhalation. They established baseline lung function and inflammation values in these animals using bronchoalveolar lavage (BAL, a procedure in which the veterinarian passes a bronchoscope through the nose into the lungs to flush fluid into a small part of the lung, collecting the fluid for examination), blood samples, and lung biopsies. Next, researchers assigned five of the horses to the antigen-avoidance group, meaning they lived in 24-hour turnout without stabling. These horses ate a grass and pellet-only diet to limit dust and mold exposure but received no other treatment.

The second group of six horses had

no housing or feed changes, remaining stabled with a hay-based diet. However, this group received daily ICS treatments of fluticasone propionate through a respirator mask covering both nostrils. Physicians commonly prescribe this drug to treat asthma, hay fever, sinusitis (sinus swelling), and rhinitis (nasal swelling) in humans.

The researchers administered a one-month weight-based loading dose consistent for all Group 2 horses. After the first month, they customized each horse's dosage to control that individual's clinical signs.

Researchers repeated lung function and inflammation measurements using BAL and blood samples after one, six, seven, and 12 months of treatment. They also took lung biopsies from all horses again at six and 12 months to record changes in inflammation based on smooth-muscle thickening measurements as well as other inflammatory markers and airway remodeling (or a structural change to the airway associated with chronic inflammation), Leclerc explained.



COURTESY DR. MATHILDE LECLERC

Researchers administered inhaled corticosteroids using respirator masks.

Clinical signs of RAO improved in horses treated with ICS but still eating hay, though lung inflammation persisted in these animals. Once moved outside, the horses' lung function continued to improve and the inflammation resolved.

The biopsy results also indicated that the thickening of the smooth muscle



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around the airways is partially reversible, even in animals that have been affected for many years, Leclerc said.

"However, avoiding hay and barn dust leads to a better control of lung inflammation and has additional beneficial

effects on pulmonary function, even when clinical signs are apparently controlled by medication," Leclerc said.

In other words, ICS treatment improved the clinical signs of RAO, much like it does with human asthma, even in the face of persistent exposure to hay dust. Antigen avoidance alone also helped reduce clinical signs, but horses received the most relief when medicated and avoiding environmental antigens.

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CT for Diagnosing Lung Disease in Foals

Veterinarians are taking a page from human medicine books as they examine applications for computed tomography (CT) in evaluating pulmonary disease in foals. Kara M. Lascola, DVM, MS, Dipl. ACVIM, an assistant professor at the University of Illinois at Urbana-Champaign College of Veterinary Medicine, described related research and potential challenges.

Computed tomography is an imaging method that creates a detailed cross-sectional picture of structures inside the body using a series of radiographs (X rays). Lascola explained that CT is the preferred imaging modality for numerous human pulmonary problems, including emphysema, acute respiratory distress syndrome, and other airway diseases. Veterinarians typically use radiography to evaluate equine neonate lungs for disease, though CT images' higher resolution can make it easier to identify pathologic (disease) processes.

Generally speaking, "current CT imaging technology allows for whole lung imaging within seconds and provides very high-quality resolution, allowing for more accurate anatomic and morphologic (structural) characterization of all components of the lung," she explained.

Pulmonary disease is a significant cause of illness and death in young foals, she said, which highlights the need for veterinarians to be able to recognize normal lung structure on CT in different species and ages. And although CT use has been widely described in dogs and cats, there's just one published report describing the use of it in horses—in an older foal.

Lascola and colleagues recently completed a pilot study, funded by the Morris Animal Foundation, using CT images to characterize lungs in healthy, sedated equine neonates breathing without assistance from a ventilator. The team found that veterinarians can perform CT imaging rapidly when foals are sedated, and the foals tolerate the procedure well. Morphologic findings included:

- All foals showed atelectasis (failure of a lung to expand properly—essentially, lung collapse).
- Foals younger than seven days old had lower volumes of normally aerated lung compared to older foals.
- The atelectasis in younger foals was considered more severe than in older foals.

EQUINE EMERGING DISEASE LUNCHEON

Tracking emerging and re-emerging equine diseases helps the horse world attempt to stay a step ahead of economically devastating and deadly outbreaks. For that reason, equine veterinarians and industry members gathered on Thursday, June 14, for Merck Animal Health's Equine Emerging and Re-Emerging Disease Luncheon at the 2013 ACVIM Forum to discuss which infectious diseases concern leading veterinarians and researchers the most.

Wendy Vaala, DVM, Dipl. ACVIM, senior equine technical veterinarian with Merck Animal Health, moderated the presentation and subsequent discussions, which covered equine coronavirus, equine protozoal myeloencephalitis, Lyme disease, equine influenza virus, and *Corynebacterium pseudotuberculosis* (the bacterium that causes pigeon fever, also known as dryland distemper).

In addition to Vaala, presenters included Nicola Pusterla, DVM, PhD, Dipl. ACVIM, of the University of California, Davis, School of Veterinary Medicine, and Amy Johnson, DVM, Dipl. ACVIM, of the University of Pennsylvania's New Bolton Center.

To read about the meeting in its entirety, see TheHorse.com/32296.—Michelle N. Anderson

While CT appears to be a useful tool for imaging equine neonates' lungs, Lascola noted that the team identified two potential limitations this modality poses in foals breathing on their own: the risk of developing atelectasis and the inability to control at which phase of breathing the image is taken.

Veterinarians have options for combating the latter issue, including controlling the foal's breathing with a manual or mechanical ventilator or opening collapsed portions of the lungs with recruitment maneuvers (sustained increases in airway pressure).

Lascola's team continues to study CT use for evaluating neonatal foals' lungs.

"We are completing a study using re-

cruitment maneuvers and positioning the foals on their back versus on their chest to minimize atelectasis," she said. "The most important things are to find a technique that is fast, safe, and clinically applicable for our patients; provides the best image quality for diagnosis; and provides other (veterinarians) who may use CT with information regarding potential limitations ... that may need to be accounted for when interpreting the images."

Equine Collapse Causes Reviewed

Unraveling the reason behind an equine collapse often presents veterinarians with a diagnostic challenge.

Neil P.H. Hudson, MA, VetMB, PhD, DEIM, DipVetClinStud, MRCVS, a senior lecturer at the University of Edinburgh's Royal (Dick) School of Veterinary Studies, reviewed with veterinarians how to evaluate a collapsed horse and listed some common diagnoses.

Usually, a veterinarian makes two types of calls to examine collapse cases: emergency visits immediately following collapse, or nonemergency visits to horses with histories of episodic collapse.

"Frustratingly, in many cases of collapse a definitive diagnosis is not reached," Hudson said.

He cited one recent study in which researchers evaluated 44 horses presented for cardiac evaluation after collapse; veterinarians weren't able to determine the cause of collapse in 18% of those horses. In another recent study of 25 horses, veterinarians determined a definitive cause of collapse in 11 cases, a presumptive diagnosis in eight cases, and no cause in



CT has proven to be a useful tool for evaluating neonatal foals' lungs.

COURTESY DR. KARA LASCOLA

the remaining six cases. And finally, in a postmortem study of 268 racehorses that collapsed and died either during work or within an hour of working, veterinarians weren't able to determine what caused collapse in 22% of cases.

When the veterinarians did find causes, they described the following:

Syncope Veterinarians use this term to describe fainting caused by a drop in arterial blood pressure leading to insufficient blood flow to the brain. The disorder remains poorly understood in horses, but its root is generally in a cardiovascular system malfunction, Hudson said, noting, "Syncope in the absence of cardiac failure is rare."

Hudson said in a recent study researchers found that syncope was either the definitive or presumed cause of 12 of 25 equine collapse cases.

He cautioned that differentiating syncope from either seizures or sleep disorders can be difficult.



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Collapse can be due to seizures, loss of motor function, and sleep disorders, among others.

Seizures Hudson said equine seizures can manifest as partial (focused in a localized area) or generalized (all-over) events and can be status epilepticus (in a state of persistent seizure, which is life-threatening). He said repeated seizures are most commonly seen in foals with an underlying disease process (acquired, such as sepsis—infection of the bloodstream) but, in some cases, can have a genetic basis. Seizures in adult horses also are largely considered acquired and generally are associated with an underlying disease process.

Hudson cited one recent study in which researchers evaluated 104 horses with histories of seizures and improved the classification system for equine seizures.

Of the 73 horses described as epileptic (having two or more recurrent seizures) in the study, Hudson said, "35.6% were classified as symptomatic (with underlying brain pathology), 54.8% were classified as cryptogenic (unknown cause), and 2.7% as idiopathic (unknown cause but with suspected genetic predisposition)."

Sleep Disorders Equine sleep disorders can also cause horses to collapse, although they're slightly different than what most

people are familiar with in humans.

"In humans, narcolepsy is characterized by chronic sleepiness, a marked disorganization of sleep/wake behavior, and pathological manifestations of rapid eye movement (REM) sleep," Hudson said, noting that narcolepsy is sometimes, but not always, associated with cataplexy (a sudden but usually brief loss of muscle tone, which causes horses to fall).

Hudson said that while narcolepsy with

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cataplexy can occur in foals and some pony breeds, sleep attacks (called idiopathic hypersomnia and characterized by excessive drowsiness, buckling at the knees, stumbling, and even total collapse) in adult horses are less likely to represent true narcolepsy.

“There is a certain degree of debate regarding nomenclature, but it is possible that some sleep attacks seen in adult horses may be a form of idiopathic

hypersomnia associated with chronic sleep deprivation,” Hudson said.

Finally, he touched briefly on three other potential causes of collapse:

■ **Coma** can be caused by trauma or by ailments including central nervous system disorders, bacterial infection, parasite infection, or liver disease.

■ **Loss of motor function** can have its source in trauma, botulism, myasthenic syndromes (abnormal muscle

weakness), and hyperkalemic periodic paralysis (commonly known as HYPP).

■ **Generalized or metabolic causes** of collapse include shock, hypoglycemia, electrolyte abnormalities, endotoxemia, and anaphylaxis.

Hudson said in the cases practitioners can pinpoint the definitive cause, they can often treat the horse successfully.

Postoperative Ileus Insights

When an owner sends a horse to go under the knife for colic surgery, first and foremost he or she is hoping the horse survives the operation. But just because the animal makes it through the procedure doesn't mean he's out of the woods: Many horses develop a dangerous complication called postoperative ileus—a lack of gut motility after surgery.

Hudson provided insight on what we know, what we're still trying to learn, and what controversies surround postoperative ileus.

Study results indicate four to 10 out of every 100 horses colic each year. And while not all of those colics are surgical cases—meaning veterinarians can successfully manage some cases medically—Hudson noted that all horses undergoing laparotomies (i.e., exploratory colic surgery) for acute abdominal crises are at risk of developing postoperative ileus.

“Postoperative ileus has been described as being responsible for between around 9% and 40% of postoperative deaths,” he explained. “Indeed, the fatality rate of postoperative ileus cases sadly can be high—ranges of 13-86% are described (in the literature).”

Researchers still aren't sure exactly what causes the condition in horses; however, they have estimated that it occurs in 10-50% of surgical colic cases, Hudson said. Scientists are exploring the disorder in a variety of species, trying to understand its pathophysiology better.

Traditionally, Hudson said, researchers believed ileus resulted from inhibited intestinal motor activity. More recently, scientists have suggested there is a significant inflammatory component, possibly triggered by the surgeon's manual manipulation of the horse's intestines. And researchers have also learned that intestinal macrophages (specialized white blood cells that kill and “clean up” damaged tissue and cells) likely play a role in developing and maintaining ileus, he said.



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Postoperative ileus treatment generally involves one or more mainstays, including nasogastric decompression (removing the horse's stomach contents via a nasogastric tube), fluid and electrolyte therapy, endotoxemia control (eliminating toxins in the bloodstream), infection control, pain management, prokinetic therapy (administering drugs that make the bowel move contents faster), and inflammation reduction. Hudson said individual clinicians have their go-to treatments and preferred order of application, but treatment methods most practitioners agree upon include:

■ **Fluid therapy** Hudson said fluid therapy is largely administered postoperatively, but is initiated on the operating table or even before the operation if the horse is cardiovascularly compromised.

“Postoperative ileus has been described as being responsible for between around 9% and 40% of postoperative deaths.”

DR. NEIL P.H. HUDSON

■ **Anti-inflammatory therapy** Hudson said researchers are continuing to examine inflammation's role in postoperative ileus development and maintenance; preliminary and anecdotal results have led many veterinarians to administer non-steroidal anti-inflammatory drugs (NSAIDs) in these cases.

■ **Early feeding and movement** Hudson said that in humans with postoperative ileus, doctors often recommend eating to encourage intestinal motility. Likewise, some veterinarians use feeding as early as clinically possible after surgery as an attempt to counteract the effects of postoperative ileus. He said hand walking horses after colic surgery, if possible, might also help.

■ **Carboxymethylcellulose administration** Researchers have found that when surgery is performed on the small intestine, administering carboxymethylcellulose—an intestinal lubricant—during the operation could help “improve survival, potentially by reducing adhesion formation (or, adhering of the resected intestine to nearby tissues),” Hudson said. However, he cautioned, another



research group found that intraoperative carboxymethylcellulose administration was associated with a higher adhesion rate.

■ **Second surgery** Hudson said there is controversy surrounding whether and when taking the horse to a second surgery (called a relaparotomy) is beneficial. “On one side, there is the argument that an early decision to go back in and ... potentially correct a mechanical obstruction or a surgical complication may be warranted,” he said. “Counterbalancing that is the evidence that the survival rate for horses requiring relaparotomy is reduced and the complication rate is high.”

■ **Prokinetic therapy** Veterinarians' therapeutic drug of choice is most commonly lidocaine (sometimes referred to as lignocaine). Other prokinetic drugs practitioners can use include metoclopramide, erythromycin, and bethanecol, Hudson said.

Although veterinarians have made strides in understanding and managing postoperative ileus, Hudson said there is much left to learn. Questions remain about the differences between healthy and diseased tissue behavior, inflammation's role, and lidocaine's effects.

Fetal Consciousness' Impact on Equine Neonatal Health

Sometime between when the birthing process begins and when the long-legged foal takes his first wobbly steps, he transitions from an unconscious fetus to a conscious horse. Researchers believe the nature of this transition could have a significant impact on neonatal health.

John Madigan, DVM, MS, Dipl. ACVIM, ACAW, professor in the Department of Medicine and Epidemiology at the University of California, Davis, School of Veterinary Medicine, said that for many years veterinarians and researchers believed neonatal maladjustment syndrome (NMS, also known as dummy foal syndrome) was caused by pre-, intra-, or postnatal hypoxia (lack of oxygen). Oxygen deprivation can result in neurologic deficits, behavioral abnormalities, and, sometimes, death.

“Histopathologic (microscopic) evidence of cerebral hemorrhage and hypoxia

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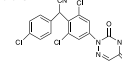
For the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

CAUTION Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

NADA #141-288 Approved by FDA

DESCRIPTION

Diclazuril, (±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzenecarboximide, has a molecular formula of C₁₇H₁₀Cl₃N₄O₂, a molecular weight of 407.64, and a molecular structure as follows:



Diclazuril is an antiprotozoal (antiprotazoal) compound with activity against several genera of the phylum Apicomplexa. PROTAZIL® (diclazuril) is supplied as oral pellets containing 1.56% diclazuril to be mixed as a top-dress in feed. Inert ingredients include dehydrated alfalfa meal, wheat middlings, cane molasses and propionic acid (preservative).

INDICATIONS

PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

DOSEAGE AND ADMINISTRATION

Dosage: PROTAZIL® (1.56% diclazuril) is administered as a top dress in the horse's daily grain ration at a rate of 1 mg diclazuril per kg (0.45 mg diclazuril/lb) of body weight for 28 days. The quantity of PROTAZIL® necessary to deliver this dose is 64 mg pellets per kg (29 mg pellets/lb) of body weight.

Administration: To achieve this dose, weigh the horse (or use a weight tape). Scoop up PROTAZIL® to the level (cup mark) corresponding to the dose for the horse's body weight using the following chart:

Weight Range of Horse (lb)	mLs of Pellets	Weight Range of Horse (lb)	mLs of Pellets
275 - 524	20	1275 - 1524	60
525 - 774	30	1525 - 1774	70
775 - 1024	40	1775 - 2074	80
1025 - 1274	50		

One 2-lb bucket of PROTAZIL® will treat one 1100-lb horse for 28 days. One 10-lb bucket of PROTAZIL® will treat five 1100-lb horses for 28 days.

CONTRAINDICATIONS

Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril.

WARNINGS

For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

PRECAUTIONS

The safe use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets with concomitant therapies in horses has not been evaluated.

ADVERSE REACTIONS

There were no adverse effects noted in the field study which could be ascribed to diclazuril.

To report suspected adverse reactions, to obtain a MSDS, or for technical assistance call 1-800-224-5318.

CLINICAL PHARMACOLOGY

The effectiveness of diclazuril in inhibiting merozoite production of *Sarcocystis neurona* and *S. falcatula* in bovine turbinate cell cultures was studied by Lindsay and Dubey (2000). Diclazuril inhibited merozoite production by more than 80% in cultures of *S. neurona* or *S. falcatula* treated with 0.1 mg/mL diclazuril and greater than 95% inhibition of merozoite production (IC₅₀) was observed when infected cultures were treated with 1.0 mg/mL diclazuril. The clinical relevance of the in vitro cell culture data has not been determined.

PHARMACOKINETICS IN THE HORSE

The oral bioavailability of diclazuril from the PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at a 5 mg/kg dose rate is approximately 5%. Related diclazuril concentrations in the cerebrospinal fluid (CSF) range between 1% and 5% of the concentrations observed in the plasma. Nevertheless, based upon equine pilot study data, CSF concentrations are expected to substantially exceed the in vitro IC₅₀ estimates for merozoite production (Dirikolu et al., 1999). Due to its long terminal elimination half-life in horses (approximately 43-65 hours), diclazuril accumulation occurs with once-daily dosing. Corresponding steady state blood levels are achieved by approximately Day 10 of administration.

EFFECTIVENESS

Two hundred and fourteen mares, stallions, and geldings of various breeds, ranging in age from 9 months to 30 years, were enrolled in a multi-center field study. All horses were confirmed EPM-positive based on the results of clinical examinations and laboratory testing, including CSF Western Blot analyses. Horses were administered PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at doses of 1.5, 5, or 10 mg diclazuril/kg body weight as a top-dress on their daily grain ration for 28 days. The horses were then evaluated for clinical changes via a modified Maynard neurological scale on Day 48 as follows:

1. Normal, neurological deficits not detected.
2. Neurological deficits may be detectable at normal gaits; signs exacerbated with manipulative procedures (e.g., backing, turning in tight circles, walking with head elevation, truncal swaying, etc.).
3. Neurological deficit obvious at normal gaits or posture; signs exacerbated with manipulative procedures.
4. Neurological deficit very prominent at normal gaits; horses give the impression they may fall (but do not) or buckle or fall with manipulative procedures.
5. Neurological deficit is profound at normal gait; horse frequently stumbles or trips and may fall at normal gaits or when manipulative procedures were utilized.
6. Horse is recumbent, unable to rise.

Each horse's response to treatment was compared to its pre-treatment values. Successful response to treatment was defined as clinical improvement of at least one grade by Day 48 ± conversion of CSF to Western Blot-negative status for *S. neurona* or achievement of Western Blot-negative CSF status without improvement of 1 ataxia grade.

Forty-two horses were initially evaluated for effectiveness and 214 horses were evaluated for safety. Clinical condition was evaluated by the clinical investigator's subjective scoring and then corroborated by evaluation of the neurological examination videotapes by a masked panel of three equine veterinarians. Although 42 horses were evaluated for clinical effectiveness, corroboration of clinical effectiveness via videotape evaluation was not possible for one horse due to missing neurological examination videotapes. Therefore, this horse was not included in the success rate calculation.

Based on the numbers of horses that seroconverted to negative Western Blot status, and the numbers of horses classified as successes by the clinical investigators, 28 of 42 horses (67%) at 1 mg/kg were considered successes. With regard to independent expert masked videotape assessments, 10 of 24 horses (42%) at 1 mg/kg were considered successes. There was no clinical difference in effectiveness among the 1.5, 5, and 10 mg/kg treatment group results.

Adverse events were reported for two of the 214 horses evaluated for safety. In the first case, a horse was enrolled showing severe neurologic signs. Within 24 hours of dosing, the horse was recumbent, biling, and exhibiting signs of dementia. The horse died, and no cause of death was determined. In the second case, the horse began walking stiffly approximately 13 days after the start of dosing. The referring veterinarian reported that the horse had been fed grass clippings and possibly had laminitis.

ANIMAL SAFETY

PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 30 horses (15 males and 15 females, ranging from 5 to 9 months of age) in a target animal safety study. Five groups of 6 horses each (3 males and 3 females) received 0, 5 (5X), 15 (15X), 25 (25X) or 50 (50X) mg diclazuril/kg (2.27 mg/lb) body weight/day for 42 consecutive days as a top-dress on the grain ration of the horse. The variables measured during the study included: clinical and physical observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, fecal analysis, necropsy, organ weights, gross and histopathologic examinations. The safety of diclazuril top-dress administered to horses at 1 mg/kg once daily cannot be determined based solely on this study because of the lack of an adequate control group (control horses tested positive for the test drug in plasma and CSF). However, possible findings associated with the drug were limited to elevations in BUN, creatinine, and SDH and less than anticipated weight gain. Definitive test article-related effects were decreased grain/top-dress consumption in horses in the 50 mg/kg group.

In a second target animal safety study, PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 24 horses (12 males and 12 females, ranging from 2 to 8 years of age). Three groups of 4 horses/sex/group received 0, 1, or 5 mg diclazuril/kg body weight/day for 42 days as a top-dress on the grain ration of the horse. The variables measured during the study included physical examinations, body weights, food and water consumption, hematology, and serum chemistry. There were no test article-related findings seen during the study.

STORAGE INFORMATION

Store between 15°C to 30°C (59°F to 86°F).

HOW SUPPLIED

PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are supplied in 2-lb (0.9 kg) and 10-lb (4.5 kg) buckets.

REFERENCES

1. Lindsay, D. S., and Dubey, J. P. 2000. Determination of the activity of diclazuril against *Sarcocystis neurona* and *Sarcocystis falcatula* in cell cultures. *J. Parasitology* 86(1):164-166.
2. Dirikolu, L., Lehner, F., Natrass, B. G., Woods, W. C., Carter, W. E., Karpiesiak, M., Jacobs, J., Boyles, J., Harkins, J. D., Grandner, D. E. and Tobin, T. 1999. Diclazuril in the horse: Its identification and detection and preliminary pharmacokinetics. *J. Vet. Pharmacol. Therap.* 22:374-379.

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has been detected in (samples from) some severely affected foals in the mid-1970s," Madigan said. "However, many foals in recent studies do not have histological evidence of hypoxia, edema (fluid swelling), or hemorrhage." Additionally, he noted, about 80% of foals with NMS fully recover; unlike hypoxic human infants, who retain neurologic deficits.

These disparities prompted Madigan to take a closer look at what causes NMS.

He and colleagues began by looking at steroids with important neuromodulatory roles, called 5alpha-reduced pregnanes (such as progestogens), which are often referred to as neurosteroids. He explained that foals are subjected to high levels of progestogens while in the dam's uterus; these steroids essentially keep the foal in a quiet state to prevent damage to the mare.

"Neonatal foals have high concentrations of pregnanes at birth, which begin to

decrease rapidly within an hour of birth and continue to decline over the first 24-48 hours of life," Madigan said. "Compared to healthy age-matched neonatal foals, NMS foals show significant ongoing elevation of plasma pregnane concentrations."

Madigan and colleagues administered a pregnane called allopregnanolone to healthy equine neonates in an experimental setting to produce clinical signs consistent with NMS. These effects were short-lasting, and foals returned to normal after administration ceased, he said.

Madigan said that while the team administered allopregnanolone, they used an electroencephalogram (EEG) to evaluate electrical impulses in the foals' brains. He said the foals' readings as they were standing were consistent with slow wave sleep.

"These data suggest that these steroids can cross the blood-brain barrier and exert neuromodulatory effects, which at high concentrations may have a dampening effect in the central nervous system with resulting alterations in states of consciousness, altered behavior, and responsiveness to stimuli, such as observed in NMS cases," Madigan said.

“There must be a clear and reliable signal that it is safe for the foal to wake up, to transition the consciousness.”

DR. JOHN MADIGAN

He hypothesized that a possible reason neurosteroids might persist and prompt NMS-like signs in some foals is that normal signaling events during the birthing process don't take place properly. For instance, he said, if a foal passes rapidly through the birth canal or is delivered via cesarean section, normal transition signals prompting reduced fetal pregnane levels might not take place, leaving the foal with elevated neurosteroid levels.

"There must be a clear and reliable signal that it is safe for the foal to wake up, to transition the consciousness," he said.

Another theory, he said, is that some neonates revert to fetal-like brain status in response to adverse effects after birth.

"Based on these findings, the concept of reducing post-birth circulating plasma



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pregnanes would seem to offer a potential new therapeutic option for NMS foals and perhaps other ill foals which appear weak and are not nursing,” Madigan said.

His team is also evaluating the possible use of a technique he and his colleagues developed called squeeze-induced somnolence, which is believed to mimic passage through the birth canal. Madigan said this method might signal to the foal that he is outside the uterus and that it's time for pregnane production to decrease, allowing him to stand, nurse, and run. Squeeze-induced somnolence involves applying pressure to the thoracic (chest) area in healthy foals to induce recumbency, non-rapid eye movement sleep, muscle relaxation, and increased beta-endorphin levels.

During their studies the team noted a unique hormone surge after 20 minutes of squeezing, which is about the amount of time a foal is squeezed in the birth canal during a normal delivery, Madigan said. The internal signal for the foal to “wake up” involves the hypothalamic pituitary adrenal axis, which the team believes downregulates the pregnane secretion so the foal can transition to birth consciousness.

Madigan and colleagues are continuing research on the mechanisms behind NMS and possible treatments. A better understanding of this phenomenon could lead to rapid management in the field and less need for intensive care of dummy or ill foals.

Box Elder Tree Seeds Linked to Seasonal Pasture Myopathy

A horse starts showing stiffness and a reluctance to move. His muscles suddenly become weak to the point he can no longer remain standing. Then, as quickly as clinical signs set in, the horse dies.

Just 48 hours earlier the horse grazed happily in his pasture—an overgrazed field full of seed heads and dead leaves.

This story is typical of suspected cases of seasonal pasture myopathy (SPM), a highly fatal muscle disease described in the Midwestern United States and Eastern Canada, and atypical myopathy (AM) in the United Kingdom and the rest of Europe. For decades the disease had baffled veterinarians on both continents, who struggled to pinpoint and agree on a cause.

That changed in 2011 when Stephanie Valberg, DVM, Dipl. ACVIM, and a team of researchers from University of Minnesota



ANNE M. EBERHARDT

The neonate's transition from an unconscious fetus to a conscious foal is a critical step.

(UM) and Iowa State University (ISU) started investigating SPM cases and found a link to box elder trees.

Valberg said SPM and AM outbreaks vary year to year and usually occur in the fall. “Horses that develop SPM and AM are usually kept on sparse pastures with an accumulation of dead leaves, dead wood, and trees in or around the pastures,” she explained.

In their study, Valberg and her team looked at 12 SPM cases that occurred at 11 Midwestern farms. Of the 12 cases, the team defined two as suspect and 10 as confirmed.

The team visited the farms located in Iowa and Minnesota, taking photos of pastures, plants, and trees. Team members also noted information about pasture topography, any overgrazing, and whether the pastures contained dead wood or standing water. They obtained photos from farms included in the study located outside of those two states, Valberg said.

A control group for the study included 23 Minnesota farms with no history of SPM in resident horses.

The farms with SPM cases all had one thing in common: the presence of box elder trees (belonging to the *Acer* family) “laden with seeds,” Valberg said. Horses with SPM at all the affected farms also were on 24-hour turnout, “which was significantly longer than horses on the control farms,” and all SPM pastures were overgrazed.

Researchers found that control farms were less likely to have box elders (61%

Regu-Mate® (altrenogest)

Solution 0.22% (2.2 mg/mL)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Regu-Mate® (altrenogest) Solution 0.22% contains the active synthetic progestin, altrenogest. The chemical name is 17 α -allyl-17 β -hydroxyestra-4,9,11-trien-3-one. The CAS Registry Number is 850-52-2. The chemical structure is:

Each mL of Regu-Mate® (altrenogest) Solution 0.22% contains 2.2 mg of altrenogest in an oil solution.

ACTIONS: Regu-Mate® (altrenogest) Solution 0.22% produces a progestational effect in mares.

INDICATIONS: Regu-Mate® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares.

Suppression of estrus allows for a predictable occurrence of estrus following withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

CONTRAINDICATIONS: Regu-Mate® (altrenogest) Solution 0.22% is contraindicated for use in mares having a previous or current history of uterine inflammation (i.e., acute, subacute, or chronic endometritis). Natural or synthetic gonadotropin therapy may exacerbate existing low-grade or “smoldering” uterine inflammation into a fulminating uterine infection in some instances.

PRECAUTIONS: Various synthetic progestins, including altrenogest, when administered to rats during the embryonic stage of pregnancy at doses manyfold greater than the recommended equine dose caused fetal anomalies, specifically masculinization of the female genitalia.

DOSAGE AND ADMINISTRATION: While wearing protective gloves, remove shipping cap and seal; replace with enclosed plastic dispensing cap. Remove cover from bottle dispensing tip and connect luer lock syringe (without needle). Draw out appropriate volume of Regu-Mate solution. (Note: Do not remove syringe while bottle is inverted as spillage may result.) Detach syringe and administer solution orally at the rate of 1 mL per 110 pounds body weight (0.044 mg/kg) once daily for 15 consecutive days. Administer solution directly on the base of the mare's tongue or on the mare's usual grain ration. Replace cover on bottle responding to prevent leakage. Excessive use of a syringe may cause the syringe to stick; therefore, replace syringe as necessary.

WHICH MARES WILL RESPOND TO REGU-MATE® (altrenogest) SOLUTION 0.22%: Extensive clinical trials have demonstrated that estrus will be suppressed in approximately 95% of the mares within three days; however, the post-treatment response depended on the level of ovarian activity when treatment was initiated. Estrus in mares exhibiting estrus cycles during the breeding season will be suppressed during treatment; these mares return to estrus four to five days following treatment and continue to cycle normally. Mares in winter anestrus with small follicles continued in anestrus and failed to exhibit normal estrus following treatment.

Response in mares in the transition phase between winter anestrus and the summer breeding season depended on the degree of follicular activity. Mares with inactive ovaries and small follicles failed to respond with normal cycles post-treatment, whereas a higher proportion of mares with ovarian follicles 20 mm or greater in diameter exhibited normal estrus cycles post-treatment. Regu-Mate® (altrenogest) Solution 0.22% was very effective for suppressing the prolonged estrus behavior frequently observed in mares during the transition period (February, March and April). In addition, a high proportion of these mares responded with regular estrus cycles post-treatment.

SPECIFIC USES FOR REGU-MATE® (altrenogest) SOLUTION 0.22%:

SUPPRESSION OF ESTRUS TO:

1. Facilitate attainment of regular cycles during the transition period from winter anestrus to the physiological breeding season. To facilitate attainment of regular cycles during the transition phase, mares should be examined to determine the degree of ovarian activity. Estrus in mares with inactive ovaries (no follicles greater than 20 mm in diameter) will be suppressed but these mares may not begin regular cycles following treatment. However, mares with active ovaries (follicles greater than 20 mm in diameter) frequently respond with regular post-treatment estrus cycles.
2. Facilitate management of the mare exhibiting prolonged estrus during the breeding season. Estrus will be suppressed in mares exhibiting prolonged behavioral estrus either early or late during the transition period. Again, the post-treatment response depends on the level of ovarian activity. The mare with greater ovarian activity initiate regular estrus and conceive sooner than the inactive mares. Regu-Mate® (altrenogest) Solution 0.22% may be administered early in the transition period to suppress estrus in mares with inactive ovaries to aid in the management of these mares or to mares later in the transition period with active ovaries to prepare and schedule the mare for breeding.
3. Permit scheduled breeding of mares during the physiological breeding season. To permit scheduled breeding, mares which are regularly cycling or which have active ovarian function should be given Regu-Mate® (altrenogest) Solution 0.22% daily for 15 consecutive days beginning 30 days before the date of the planned estrus. Ovulation will occur 5 to 7 days following the onset of estrus as expected for nontreated mares. Breeding should follow usual procedures for mares in estrus. Mares may be regulated and scheduled either individually or in groups.

ADDITIONAL INFORMATION: A 3-year well controlled reproductive safety study was conducted in 27 pregnant mares, and compared with 24 untreated control mares. Treated mares received 2 mL Regu-Mate® (altrenogest) Solution 0.22% (1.0 to body weight) (2x dosage recommended for estrus suppression) from day 20 to day 325 of gestation. This study provided the following data:

1. Full offspring (all ages) of treated mares, clinical size was increased.
2. Foal offspring from treated mares had shorter interval from Feb. 1 to first ovulation than fillies from their untreated mare counterparts.
3. There were no significant differences in reproductive performance between treated and untreated animals (mares & their respective offspring) measuring the following parameters:
 - interval from Feb. 1 to first ovulation, in mares only;
 - mean interval from first to second cycle and second to third cycle, mares only;
 - follicle size, mares only;
 - at 50 days gestation, pregnancy rate in treated mares was 81.8% (9/11) and untreated mares was 100% (4/4);
 - after 3 cycles, 11/12 treated mares were pregnant (92.7%) and 4/4 untreated mares were pregnant (100%);
 - colt offspring of treated and control mares reached puberty at approximately the same age (82 & 84 weeks respectively);
 - stallion offspring from treated and control mares showed no differences in seminal volume, spermatozoal concentration, spermatozoal motility, and total sperm per ejaculate.
 - stallion offspring from treated and control mares showed no differences in behavior.
 - testicular characteristics (scrotal width, testis weight, parenchymal weight, epididymal weight and height, testicular height, width & length) were the same between stallion offspring of treated and control mares.

REFERENCES:

Shoenmaker, C.F., E.L. Squires, and R.K. Shideler. 1989. Safety of Altrenogest in Pregnant Mares and on Health and Development of Offspring. Eq. Vet. Sci. (9): No. 2: 69-72.

Squires, E.L., R.K. Shideler, and A.O. McKinnon. 1989. Reproductive Performance of Offspring from Mares Administered Altrenogest During Gestation. Eq. Vet. Sci. (9): No. 2: 73-76.

WARNING: Do not use in horses intended for feed.

HUMAN WARNINGS: Skin contact must be avoided as Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed through unbroken skin. Protective gloves must be worn by all persons handling this product. Pregnant women or women who suspect they are pregnant should not handle Regu-Mate® (altrenogest) Solution 0.22%. Women of child bearing age should use extreme caution when handling this product. Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

INFORMATION FOR HANDLERS:

WARNING: Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed by the skin. Skin contact must be avoided; protective gloves must be worn when handling this product.

Effects of Overexposure: There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmacological class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest. Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed. In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT:

1. Women who are or suspect they are pregnant.
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events.
3. Anyone with cerebral vascular or coronary artery disease.
4. Women with known or suspected carcinoma of the breast.
5. People with known or suspected estrogen-dependent neoplasia.
6. Women with undiagnosed vaginal bleeding.
7. People with benign or malignant tumors which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

ACCIDENTAL EXPOSURE: Altrenogest is readily absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Altrenogest should not penetrate plastic rubber covered gloves; however, if there is leakage (i.e., pinholes, spillage, etc.) the contaminated area covered by such occlusive materials may have increased absorption. The following measures are recommended in case of accidental exposure.

First Aid: Wash immediately with soap and water.
Eye Exposure: Immediately flush with plenty of water for 15 minutes. Get medical attention.
If Swallowed: Do not induce vomiting. Regu-Mate® (altrenogest) Solution 0.22% contains an oil. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage due to aspiration of the oil base. If possible, bring the container and labeling to the physician.

CAUTION: For oral use in horses only. Keep this and all medication out of the reach of children.

Store at or below 25°C (77°F).

NADA# 131-310, Approved by FDA.

HOW SUPPLIED:

Regu-Mate® (altrenogest) Solution 0.22% (2.2 mg/mL).

Each mL contains 2.2 mg altrenogest in an oil solution.

Available in 1000 mL plastic bottles.

* US Patents 3,453,267; 3,478,067; 3,484,462

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compared to 100%). Additionally, they were less likely to have overgrazed pastures (44% compared to 100%). Horses at SPM farms were less likely to receive supplemental hay or concentrate than those at the control farms, Valberg said.

"Thus, the common features for SPM horses were little supplemental feeding and prolonged grazing of sparse pastures that were in close proximity to seed-laden box elder trees," she said.

The research team collected box elder seed samples randomly from seven of the 11 SPM farms during fall 2011, as well as a control sample of ash tree seeds. Testing found that one nonproteogenic amino acid, hypoglycin A, was "highly abundant" in the box elder seeds but not in ash seeds. This amino acid is known to block the same enzyme in fat metabolism in humans as was detected in SPM-afflicted horses.

Recently, scientists have found a related

tree, the European sycamore maple tree (*Acer pseudoplatanus*), in northern European pastures where horses have died from AM, Valberg said. European sycamore maple seeds also contain hypoglycin A.

"Hypoglycin A is a common cause of both SPM and AM," Valberg concluded. "This is supported by common epidemiology of SPM and AM, a common block on fat metabolism, the presence of hypoglycin-A-containing *Acer* species in affected pastures, and the presence of the toxic principle of hypoglycin A in the bloodstream of afflicted horses."

Young horses and those new to an affected pasture appear to be at great risk if:

- Pastures are overgrazed in the fall and early spring;
- Turnout time is greater than 12 hours per day; and
- No supplemental hay is provided on pasture.

Valberg noted that some horses do not develop SPM even after years of living on affected pastures.

To address owners' concerns of SPM developing in their horses, Valberg suggested removing box elder or European sycamore trees from affected pastures, although "this might not always be feasible."

In cases where the trees can't be removed, Valberg recommended decreasing turnout time on affected pastures from October through mid-December and in the early spring.

"Other important preventive measures could include providing additional forage



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COURTESY DR. STEPHANIE VALBERG

Farms with SPM-affected horses all contained box elder trees laden with seeds.

if pastures are overgrazed, preventing overgrazing of pastures through rotational grazing, and limiting turnout to less than 12 hours per day during fall and early spring," she said.

More research is necessary to determine if seasonal and annual fluctuations occur in box elder and sycamore maple trees' hypoglycin A content, she said.

Botulism in Horses: An Update

Rising hay prices and the financial crunch caused by 2009's recession drove many horse owners to seek less expensive forage sources, including large round bales, haylage, and silage. But according to Amy Johnson, DVM, Dipl. ACVIM, compromising on hay quality and feeding from half-ton bales led to a larger problem: an uptick in reported botulism cases.

Johnson, who studies the disease at the University of Pennsylvania's National Botulism Reference Laboratory, described advances in diagnosing botulism in horses.

Botulism is a highly fatal multispecies neurologic disease caused by the bacterium *Clostridium botulinum* and the toxin it produces. The Centers for Disease Control and Prevention classifies it as a Category A (highest priority/highest risk) agent because it's a food-safety concern for humans and poses a real risk as a bioterrorism weapon for use against human and animal populations.

Despite their large size, horses are the most susceptible species to botulism toxicity, making them an important piece in understanding the botulism puzzle.

There are seven known strains of *C. botulinum*, described as Types A through G. Types A and B are most common in horses and are usually acquired through forage sources, Johnson said, adding that Type C is caused by carrion exposure (i.e., a decaying dead animal in feed). Type B is the only strain for which a vaccine is marketed for use in horses. Types D through G have never been reported in U.S. horses.

Johnson reviewed the three ways horses can contract botulism:

- Ingesting the botulinum toxin produced by *C. botulinum*;
- Foals—which have immature digestive tracts unable to protect them from the bacteria—ingesting *C. botulinum* spores that grow and subsequently elaborate toxin, leading to "shaker" syndrome; and
- Wound contamination.

A mouse bioassay is the species-wide

"gold standard" for diagnosing botulism. In the simplest terms, this test exposes mice to samples from patients showing signs of botulism. If the sample contains botulism neurotoxin, and the mouse dies as a result, the horse likely has botulism. However, the mouse bioassay test takes time (anywhere from five days to two to three weeks, depending on the sample), and time is something a horse with botulism doesn't have, Johnson said.

"Laboratory confirmation with the mouse bioassay can be difficult," she said. False negative results are common because it takes very little toxin to cause botulism in a horse, and what little toxin there is does not remain in the gastrointestinal tract or bloodstream for long.

Experienced practitioners often base diagnosis on a horse's clinical signs and case history. Pertinent case history information includes whether the horse lives in an endemic area and the animal's current vaccination status against botulism Type B. Evaluation of feeding practices is also important because horses fed from large bales or with haylage or silage are more likely to contract botulism. Carrion exposure is also an important factor.

Johnson described the following two tests for botulism:

■ **Tongue tone or tongue stress test.** For this test, the veterinarian gently pulls the horse's tongue from its mouth. The examiner then holds the horse's jaw shut and assesses the animal's ability to retract his tongue into his mouth.

■ **Grain test.** In this test the horse is fed about eight ounces of sweet feed in a pan. "A normal horse can eat that amount of grain in less than two minutes, some faster," Johnson said. "Horses with botulism can take 15 minutes, and even then might not finish it."

Botulism treatment includes a combination of antitoxin administration and supportive care. Veterinarians should give the horse antitoxin as soon as clinical signs and case history point toward botulism. "Every hour of delay reduces chances of survival," she stressed.

At this time horses can also receive the botulism Type B vaccine, Johnson said. Unlike with some diseases, natural exposure to *C. botulinum* toxin does not reliably stimulate the horse's immune system to produce protective antibodies. Vaccinating the horse with the Type B *C. botulinum*

Regu-Mate® (altrenogest)

Solution 0.22% (2.2 mg/mL)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Regu-Mate® (altrenogest) Solution 0.22% contains the active synthetic progestin, altrenogest. The chemical name is 17 α -allyl-17 β -hydroxyestra-4,9,11-trien-3-one. The CAS Registry Number is 850-52-2. The chemical structure is:

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ACTIONS: Regu-Mate® (altrenogest) Solution 0.22% is a progestational agent in mares.

INDICATIONS: Regu-Mate® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares. Suppression of estrus allows for a predictable occurrence of estrus following withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

CONTRAINDICATIONS: Regu-Mate® (altrenogest) Solution 0.22% is contraindicated for use in mares having a previous or current history of uterine inflammation (i.e., acute, subacute, or chronic endometritis). Natural or synthetic gonadotropin therapy may exacerbate existing low-grade or "smoldering" uterine inflammation into a fulminating uterine infection in some instances.

PRECAUTIONS: Various synthetic progestins, including altrenogest, when administered to rats during the embryonic stage of pregnancy at doses manyfold greater than the recommended equine dose caused fetal anomalies, specifically masculinization of the female genitalia.

DOSAGE AND ADMINISTRATION: While wearing protective gloves, remove shipping cap and seal; replace with enclosed plastic dispensing cap. Remove cover from bottle dispensing tip and connect luer lock syringe (without needle). Draw out appropriate volume of Regu-Mate solution. (Note: Do not remove syringe while bottle is inverted as spillage may result.) Detach syringe and administer solution orally at the rate of 1 mL per 110 pounds body weight (0.044 mg/kg) once daily for 15 consecutive days. Administer solution directly on the base of the mare's tongue or on the mare's usual grain ration. Replace cover on bottle responding to prevent leakage. Excessive use of a syringe may cause the syringe to stick; therefore, replace syringe as necessary.

WHICH MARES WILL RESPOND TO REGU-MATE® (altrenogest) SOLUTION 0.22%? Extensive clinical trials have demonstrated that estrus will be suppressed in approximately 95% of the mares within three days; however, the post-treatment response depended on the level of ovarian activity when treatment was initiated. Estrus in mares exhibiting regular estrus cycles during the breeding season will be suppressed during treatment; these mares return to estrus four to five days following treatment and continue to cycle normally. Mares in winter anestrus with small follicles continued in anestrus and failed to exhibit normal estrus cycles following treatment.

Response in mares in the transition phase between winter anestrus and the summer breeding season depended on the degree of follicular activity. Mares with inactive ovaries and small follicles failed to respond with normal cycles post-treatment, whereas a higher proportion of mares with ovarian follicles 20 mm or greater in diameter exhibited normal estrus cycles post-treatment. Regu-Mate® (altrenogest) Solution 0.22% was very effective for suppressing the prolonged estrus behavior frequently observed in mares during the transition period (February, March and April). In addition, a high proportion of these mares responded with regular estrus cycles post-treatment.

SPECIFIC USES FOR REGU-MATE® (altrenogest) SOLUTION 0.22%:

SUPPRESSION OF ESTRUS TO:

1. Facilitate attainment of regular cycles during the transition period from winter anestrus to the physiological breeding season. To facilitate attainment of regular cycles during the transition phase, mares should be examined to determine the degree of ovarian activity. Estrus in mares with inactive ovaries (no follicles greater than 20 mm in diameter) will be suppressed but these mares may not begin regular cycles following treatment. However, mares with active ovaries (follicles greater than 20 mm in diameter) frequently respond with regular post-treatment estrus cycles.

Facilitate management of the mare exhibiting prolonged estrus during the transition period. Estrus will be suppressed in mares exhibiting prolonged estrus behavior either early or late during the transition period. Again, the post-treatment response depends on the level of ovarian activity. The response in mares with greater ovarian activity initiate regular estrus cycles and conceive sooner than the inactive mares. Regu-Mate® (altrenogest) Solution 0.22% may be administered early in the transition period to suppress estrus in mares with inactive ovaries to aid in the management of these mares or to mares later in the transition period with active ovaries to prepare and schedule the mare for breeding.

3. Permit scheduled breeding of mares during the physiological breeding season. To permit scheduled breeding, mares which are regularly cycling or which have active ovarian function should be given Regu-Mate® (altrenogest) Solution 0.22% daily for 15 consecutive days beginning 30 days before the date of the planned estrus. Ovulation will occur 5 to 7 days following the onset of estrus as expected for untreated mares. Breeding should follow usual procedures for mares in estrus. Mares may be regulated and scheduled either individually or in groups.

ADDITIONAL INFORMATION: A 3-year well controlled reproductive safety study was conducted in 27 pregnant mares, and compared with 24 untreated control mares. Treated mares received 2 mL

Regu-Mate® (altrenogest) Solution 0.22% (1.0 lb body weight) (2x dosage recommended for estrus suppression) from day 20 to day 325 of gestation. This study provided the following data:

1. Filly offspring (all ages) of treated mares, clinical size was treated.

2. Filly offspring from treated mares had shorter interval from Feb. 1 to first ovulation than fillies from their untreated mare counterparts.

3. There were no significant differences in reproductive performance between treated and untreated animals (mares & their respective offspring) measuring the following parameters:

- interval from Feb. 1 to first ovulation, in mares only;
- mean interval between first to second cycle and second to third cycle, in mares only;
- follicle size, mares only;
- at 50 days gestation, pregnancy rate in treated mares was 81.8% (9/11) and untreated mares was 100% (4/4);
- after 3 cycles, 11/12 treated mares were pregnant (92.7%) and 4/4 untreated mares were pregnant (100%);
- colt offspring of treated and control mares reached puberty at approximately the same age (62 & 64 weeks respectively);
- stallion offspring from treated and control mares showed no differences in seminal volume, spermatozoal concentration, spermatozoal motility, and total sperm per ejaculate.
- stallion offspring from treated and control mares showed no differences in sexual behavior.
- testicular characteristics (scrotal width, testis weight, parenchymal weight, epididymal weight and height, testicular length, width & length) were the same between stallion offspring of treated and control mares.

REFERENCES:

Shoemaker, C.F., E.L. Squires, and R.K. Shideler. 1989 Safety of Altrenogest in Pregnant Mares and on Health and Development of Offspring. Eq. Vet. Sci. (9): No. 2: 69-72.

Squires, E.L., R.K. Shideler, and A.O. McKinnon. 1989 Effect of Altrenogest on Performance of Offspring from Mares Administered Altrenogest During Gestation. Eq. Vet. Sci. (9): No. 2: 73-76.

WARNING: Do not use in horses intended for feed.

HUMAN WARNINGS: Skin contact must be avoided as Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed through unbroken skin. Protective gloves must be worn by all persons handling this product. Pregnant women or women who suspect they are pregnant should not handle Regu-Mate® (altrenogest) Solution 0.22%. Women of child bearing age should avoid contact with this product when handling this product. Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

INFORMATION FOR HANDLERS:

WARNING: Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed by the skin. Skin contact must be avoided; protective gloves must be worn when handling this product.

Effects of Overexposure: There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmaceutical class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest. Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed. In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT:

1. Women who are or suspect they are pregnant.
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events.
3. Anyone with cerebral vascular or coronary artery disease.
4. Women with known or suspected carcinoma of the breast.
5. People with known or suspected estrogen-dependent neoplasia.
6. Women with undiagnosed vaginal bleeding.
7. People with benign or malignant tumors which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

ACCIDENTAL EXPOSURE: Altrenogest is readily absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Altrenogest should not penetrate plastic rubber or impervious gloves; however, if there is leakage (i.e., pinholes, spillage, etc.), the contaminated area covered by such occlusive materials may have increased absorption. The following measures are recommended in case of accidental exposure.

Skin Exposure: Wash immediately with soap and water.

Eye Exposure: Immediately flush with plenty of water for 15 minutes. Get medical attention.

If Swallowed: Do not induce vomiting. Regu-Mate® (altrenogest) Solution 0.22% contains an oil. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage via aspiration of the oil base. If possible, bring the container and labeling to the physician.

CAUTION: For oral use in horses only. Keep this and all medication out of the reach of children.

Store at or below 25°C (77°F).

NADA# 131-310, Approved by FDA.

HOW SUPPLIED:

Regu-Mate® (altrenogest) Solution 0.22% (2.2 mg/mL).

Each mL contains 2.2 mg altrenogest in an oil solution.

Available in 1000 mL plastic bottles.

* US Patents 3,453,267; 3,478,067; 3,484,462

Manufactured by:

DPT Laboratories, San Antonio, TX 78215

Distributed by:

Intervet Inc., Millisboro, DE 19966

ANIMAL SURVIVOR Q

Trainer Julie Blacklow thought Q's quiet demeanor and willing attitude had to do with her team's excellent training skills at Rosebud River Ranch in Snoqualmie, Wash. In reality, the yearling Rocky Mountain Saddle Horse gelding was critically sick with proliferative enteropathy, a disease caused by the bacterium *Lawsonia intracellularis* and something Blacklow, a veteran horsewoman, had never heard of. She's not alone.

The American College of Veterinary Internal Medicine (ACVIM) is trying to change that by making owners more aware of *L. intracellularis* in horses. At the 2013 ACVIM Forum, the organization introduced Q as part of its "Animal Survivor" program, which highlights animals that—thanks to advances in veterinary internal medicine—have lived through severe disease.

Q's survival story started when he spiked a temperature of 104°F (99-101°F is normal). He also became lethargic and stopped eating, a sign to Blacklow that something was very wrong with the young horse. After an inconclusive initial exam by a general practitioner, Blacklow sought a specialist's second opinion. She contacted Chantal Rothschild, DVM, Dipl. ACVIM, of Northwest Equine Veterinary Associates, in Maple Valley, Wash.

Rothschild performed ultrasounds of Q's chest and abdomen looking for the source of the infection causing his fever. Then the gelding's blood work came back with extremely low protein levels. This is a telltale clinical sign of proliferative enteropathy, a spreading infection of the intestine most common in foals two to seven months old that renders the animal unable to absorb protein from his diet. Edema (swelling) had also developed around the horse's jaw and down into his chest.

L. intracellularis is common in pigs, and certain wild animals are thought to carry it, Rothschild said, adding that the disease is believed to be contracted when horses ingest bacteria from infected animal feces. Rothschild had treated equine cases during her time practicing in Texas and at Washington State University on the eastern edge of the state. "But I'd never seen a case in the Seattle area," she said.

After examining Q, Rothschild recommended treating him for proliferative enteropathy immediately rather than waiting for test results confirming *L. intracellularis* infection. "It would take too long to get a positive test back, so I asked the owners to trust me," Rothschild said. "If we'd waited we might not have been able to save him."

Q responded within three days and started acting less like the calm horse Blacklow knew and more like an energetic youngster.

Q's intensive treatment continued for six weeks, multiple times per day, and required dedication from the farm's workers and the horse's patience. Q was an excellent patient, Blacklow reported, and has since made what she considers a full recovery.—Michelle N. Anderson



COURTESY ACVIM

Q survived a severe case of proliferative enteropathy.

toxoid vaccine reliably induces a protective immune response and prevents future susceptibility to botulism, she said. "Unfortunately, there is no cross-protection between types, so the Type B vaccine will only protect against Type B botulism and not against Types A or C," she said.

Antitoxin prevents additional botulism toxins from binding to their target, halting progression of the disease, but it does not reverse the disease or treat clinical signs. "So you should expect the horse to get a little bit worse before getting better," Johnson said.

Supportive care includes management of the down horse, hydration, and nutrition, Johnson said. She described recumbent horses with botulism as "Swiffers," because they are very susceptible to "picking up" environmental contamination and as such become very susceptible to nosocomial (hospital-acquired) infections. She said they are also susceptible to developing pressure sores and secondary infection, even when receiving high-quality care.

Practitioners and nursing staff should not force horses to rise frequently or stand for prolonged periods, Johnson said,

because doing so can weaken the horse and cause clinical signs to worsen.

She also doesn't recommend sling support in the first one to three days of treatment. "However, after antitoxin treatment and stabilization of signs some severely affected horses will benefit from use of a sling to assist them to rise," she said.

In addition to pressure sores, complications in severely affected horses can include cellulitis (a diffuse inflammation resulting from infection of deep connective tissue), myositis (muscle inflammation), colic, cystitis (inflammation of the bladder), pneumonia, and salmonellosis.

A New Bolton study cites a 96% survival rate in a group of 30 shaker foals treated in the hospital and receiving antitoxin. Among the foals requiring ventilation support, 88% survived. In comparison, Johnson said in an older study researchers reported that 98% of foals not treated with antitoxin die.

Researchers haven't completed any papers on survival rates in a large group of adult horses with botulism. Based on a handful of published case reports, adult survival has been markedly lower than foal survival (90% mortality rate from Type A, 70% from Type B, and 80% from Type C), Johnson pointed out. Horses managed intensively in hospital settings have a higher survival rate, but probably not more than 50% of adult horses survive the disease.

"It's much harder to manage an adult horse with botulism," Johnson explained.

She and the other members of the National Botulism Reference Laboratory have optimized and validated polymerase chain reaction (PCR) techniques to detect the neurotoxin gene of *C. botulinum* in samples from equine cases of botulism.

The PCR assays identify the three clinically relevant types (Types A, B, and C) and offer several benefits over the mouse bioassay. "Results are available more quickly, the false negative rate is lower, and no lab animals are used," she said.

Additional objectives include finding, optimizing, and validating a test that detects the *C. botulinum* neurotoxin itself in equine samples, Johnson said, adding that "if such a test exists, it will eliminate the need for the mouse bioassay. 🐾

ABOUT THE AUTHORS

Michelle N. Anderson is the digital editor and Erica Larson is news editor at The Horse.