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Acetaminophen For Lameness

Could Chemistry Help With Poor Performance?

Domestic Horses Healthier Than Wild Ones

Donkey Medicine: Where Are the Data?

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1 Data on file.

2 Adequan® i.m. Package Insert, Rev 1/19.

3 Burba DJ, Collier MA, DeBault LE, Hanson-Painton O, Thompson HC, Holder CL: In vivo kinetic study on uptake and distribution of intramuscular tritium-labeled polysulfated glycosaminoglycan in equine body fluid compartments and articular cartilage in an osteochondral defect model. *J Equine Vet Sci* 1993; 13: 696-703.

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5 McIlwraith CW, Frisbie DD, Kawcak CE, van Weeren PR. Joint Disease in the Horse.St. Louis, MO: Elsevier, 2016; 33-48.

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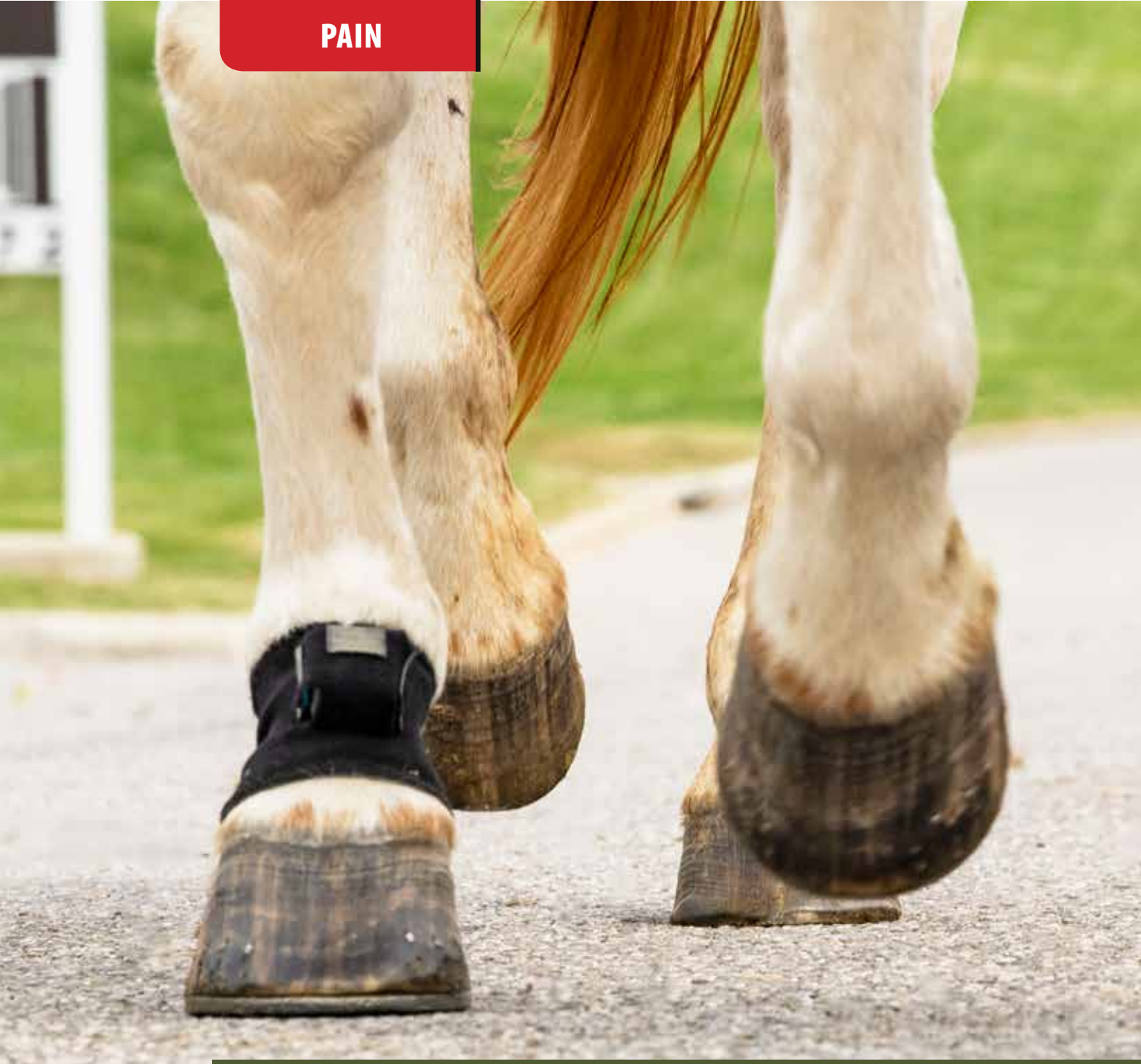

ACETAMINOPHEN:
SAFE AND EFFECTIVE FOR EQUINE LAMENESS

By Marie Rosenthal MS

More equine veterinarians are turning to acetaminophen, but is it a safe and effective treatment for equine lameness? And how much can you use?

It just might be and at a fairly large dose, according to a study done by **Melissa A. Mercer**, DVM, PhD, DACVIM-LA, and her colleagues at Virginia-Maryland College of Veterinary Medicine.

In their study, 30 mg/kg of oral acetaminophen produced a rapid improvement in lameness scores, but the finding was transient.

"Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used analgesic and antipyretic agents in equine practice," Dr. Mercer said at the 2021 AAEP Annual Convention, in Nashville, Tenn. "And I'm sure all of you here today have prescribed them to a horse or to yourself on a daily basis given the aches and pains we have with this job."

Although COX-1 inhibitors are powerful anti-inflammatories, they have multiple adverse events of concern, including gastroduodenal ulceration and right dorsal colitis. COX-2 selective inhibitors are less effective than COX-1 and have a similar adverse event profile, she said, and human COX-2 inhibitor formulations even carry FDA boxed warnings for serious adverse events.

Analgesia for Chronic Pain Needed

"Therefore, there's a need for chronic adjunctive analgesic treatment in horses with chronic orthopedic pain that is not responsive to [most NSAIDs] or which cannot tolerate long-term NSAID administration. And this is a priority for maximizing equine welfare as well as improving treatment outcomes," Dr. Mercer said.

Acetaminophen is one of the most used analgesic and antipyretic drugs in human medicine due to its high margin of safety. And it's used for many of the same applications as traditional NSAIDs, according to Dr. Mercer, even though it is a poor anti-inflammatory agent.

"And while we don't know exactly how acetaminophen works, it's postulated that it's through interactions with the endocannabinoid, opioid and serotonergic systems," she explained, producing an active metabolite that is seen in opioids and cannabis, without the euphoria seen in those drugs.

In addition, acetaminophen lacks the gastrointestinal and renal side effects of other NSAIDs, and it is safe up to 150 mg/kg/day.

"Due to its wide margin of safety and different mechanism of action, it's been used in combination with or alternating with traditional NSAID therapy in humans with great success," Dr. Mercer said, and it is preferred for people with chronic osteoarthritis pain.

Images courtesy of Dr. Melissa A. Mercer

Lameness evaluations were performed at the start of the study and 21 days after treatment.

Attractive Option

It also becoming an attractive option for horses, particularly on the farm.

Acetaminophen was first used as a marker of gastric emptying in horses because of its relatively poor absorption from the stomach and rapid absorption from the proximal .intestine. The group at Virginia-Maryland College of Veterinary Medicine found that it was comparable with flunixin meglumine in reducing fever and treating laminitis and lameness, she said.

"We've previously published a study using 20 mg/kg twice daily for 14 days and found that it was safe and produced plasma concentrations that were above the proposed therapeutic margin of 10 mcg/mL," she said.

They wanted to know if a higher concentration of 30 mg/kg twice daily for 21 days would be more effective and still safe. They crushed 500-mg extra-

strength, over-the-counter acetaminophen and mixed it with a small amount of corn syrup to make it palatable for oral consumption. They wanted this to be as close to real world as possible, so they enrolled 12 adult horses with naturally occurring chronic lameness that was a minimum of 2 out of 5, according to the AAEP grade score. Lameness had been occurring for more than 4 weeks and, not in involved 1 or more limbs.

There were 7 geldings in 5 mares between 13 to 23 years of age that were maintained as part of a rescue herd. The horses maintained their normal riding program schedules throughout the study. Seven horses had osteoarthritis; 4 had navicular syndrome; 1 each had osteochondral fragments, patellar enthesopathy or lateral collateral and distal oblique sesmoidean ligament desmopathy.

There was a 7-day washout period for disease altering agents and a 30-day washout for any systemic or intraarticular corticosteroids prior to study initiation.

All horses participated in the clinical field trial, as well as the pharmacokinetics portion and the clinical pathologic data portion of the safety study. The horses were randomly selected to undergo gastroscopy or liver biopsy during the safety portion of the study.

Baseline control lameness evaluations were performed at the start of the study and 21 days after consecutive treatment. The lameness evaluation was a straight-line straw on asphalt surface led by a single handler with a lead and was videotaped for subjective lameness evaluation. In addition, body mounted inertial sensors (Lameness Locator by Equinosis) were also placed.

Blood was collected on day 7 and day 21, and the gastroscopies and liver biopsies were performed before the study treatment was given and on day 21 or 22, respectively.

Although acetaminophen was relatively safe, the improvement in chronic lameness was transient, so it might not be suitable as monotherapy.

They found that acetaminophen was rapidly absorbed with plasma concentrations reaching a peak average of 22.7 mcg/mL within an average of 0.44 hours on day 7 and a peak plasma concentration of 18.37 mcg/mL within an average of 0.71 hours on day 21, "so it is rapidly absorbed," she said.

However, it was variable. Because they wanted to recreate a regular clinical environment, the horses were allowed free choice hay and water through the study. Giving acetaminophen after a meal prolongs the time to maximum concentration, so differences were likely due to variances in gastric emptying of the horses.

No Long-Term Accumulation

There was no accumulation of acetaminophen following the 21 days of treatment, and there was a significant decrease in the total difference of head height at 1 hour post treatment for the Lameness Locator variables, according to Dr. Mercer, although other inertial sensor parameters did not see a difference between the beginning and the end of the study.

There were no significant differences in liver values or glandular mucosal ulcer group scores between day –1 and day 21. However, they did see a significant decrease in the squamous mucosal scores, probably due to the washout period for other medications.

"I'm not suggesting that acetaminophen is a treatment for gastric ulcers," she emphasized. "What I am suggesting is that it's likely that to pulling these horses off of chronic NSAID therapy for that 7-day washout before treatment with acetaminophen actually allowed them to heal their ulcers throughout the course of the study."

There was no accumulation of acetaminophen following the 21 days of treatment, and no evidence of hepatopathy or gastric ulceration after 21 days of the higher dosing, according to Dr. Mercer. However, the improvement in chronic lameness was transient, so it might not be suitable as monotherapy. **MeV**

For more information:

Mercer MA, McKenzie HC, Byron CR, et al. Pharmacokinetics and clinical efficacy of acetaminophen (paracetamol) in adult horses with mechanically induced lameness. *Equine Vet J.* 2022 May 28. doi: 10.1111/evj.13601.

DNA Test Identifies Equine Lyme Disease

By Kitta MacPherson

When the team at Cornell University School of Veterinary Medicine could not detect *Borrelia burgdorferi* in a horse with neurologic illness, a Rutgers scientist created an ultra-sensitive DNA, test that could have applications for difficult-to-detect illnesses in humans such as Lyme disease.

Steven Schutzer, MD, a professor of medicine at Rutgers New Jersey Medical School, helped the Cornell team identify neurologic Lyme disease in a sick 11-year-old Swedish Warmblood mare.

Although Lyme disease was suspected, a standard PCR test did not detect the corkscrew-shaped bacterium *B. burgdorferi.*

As with the treatment of most diseases, early detection is essential with Lyme. "Early diagnosis leads to immediate treatment," Dr. Schutzer said. "And, naturally, that gives the best chance for a cure."

The "genomic hybrid capture assay," a highly sensitive test Dr. Schutzer's team has been developing, identified the pathogen in a sample of the horse's spinal fluid, allowing it to be diagnosed and successfully treated. The test works by first selectively isolating DNA from the microorganism causing the disease.

"The method is like having a special, specific 'fishhook' that only grabs *Borrelia* DNA and not the DNA of other microbes, nor the DNA of the host (animal or human)," Dr. Schutzer said. "Detecting DNA of the disease is a direct test, meaning we know you have active disease if it's circulating in the blood or spinal fluid."

Lyme disease is the most common vector-borne illness in the United States, according to the CDC. Horses are incidental, dead-end hosts for *B. burgdorferi*, meaning the hosts carry the infection but do not infect others. Not all infected horses develop clinical signs of Lyme disease. If symptoms occur, they can include chronic weight loss, lameness and low-grade fever. Antibody tests usually are administered when a Lyme disease infection is suspected.

However, in this case, an antibody test and a PCR test of the mare didn't indicate an infection. Only Dr. Schutzer's advanced test detected the disease.

Lyme disease in horses can cause long-term complications that include damage to the nervous system, joints, skin and vision.

"The diagnosis of Lyme neuroborreliosis in horses is rarely confirmed antemortem and has frustrated veterinarians for years," said **Thomas Divers,** DVM, a professor of medicine and co-chief of the Section of Large Animal Medicine at Cornell in New York. "This is a very promising technique. Focused treatment against *B. burgdorferi* administered in this case resulted in the horse's complete athletic recovery."

While many illnesses, such as COVID-19 and strep throat, attack humans with many numbers of pathogens, in other diseases, such as Lyme disease, the bacteria slowly reproduce within a host, producing far fewer numbers and making detection more difficult.

Dr. Schutzer, an expert in Lyme and other tick-borne diseases, has been working to devise ways to better detect diseases that possess what he terms "low copy numbers" of a pathogen. **MeV**

READ MORE from Dr. Divers about interpreting chemistries on page 14.

For more information:

Divers TJ, Mongodin EF, Miller BC, et al. Genomic hybrid capture assay to detect *Borrelia burgdorferi*: an application to diagnose neuroborreliosis in horses. *J Vet Diagn Invest.* 2022 Jul 21. 104063872211126 DOI: 10.1177/10406387221112617

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[1]Equine Veterinarian Practice Passion & Practice Study Presentation, conducted by ASQ360° on behalf of CareCredit, December 2020.
[2]CareCredit Path to Care, Pet Care Findings, conducted by Chadwick Martin Bailey on behalf of CareCredit, October 2021.

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Long-Term Relationships Good for Horses, Too

Horses may be more reluctant in new situations if they have a shorter relationship with their owners, multiple handlers or numerous owner-changes. These factors could negatively affect the horse-human interactions in new situations.

Horses have been living with humans for thousands of years. Following this long co-evolution, horses today demonstrate impressive social skills during their interactions with humans. They are: receptive to human emotions and very good at understanding human demands.

Yet, some horses are more skittish than others, and researchers wanted to know why. An international research team from the University of Turku and the University of Helsinki in Finland, and the INRAE of Nouzilly in France, studied the interactions between horses and humans, as well as how horses react in new situations.

The researchers recruited 76 privately owned leisure horses from the Turku area to perform 2 behavioral tests to observe the horses' reactions to novel objects. In addition, the researchers studied whether the horse reacted differently when it faced the new object with a familiar owner or with a stranger, i.e., the researcher.

The horses were led to walk on 2 surfaces that were new to them; a white tarp, and a fluffy blanket. They were led to 1 of the surfaces by their owner and to the other by an unfamiliar researcher.

Second, the horses were presented with a fluffy stuffed toy either by their owner or by an unfamiliar researcher. The horse had 1 minute to freely come and interact with the toy and then the person approached the horse and tried to touch its neck with the toy.

"Interestingly, horses with an exclusive relationship with their owner were the calmest when approaching the novel surfaces and easily agreed to be touched with the toy. Horses that are regularly ridden or trained by different people showed more stress behaviors in the test situations," said **Océane Liehrmann**, a doctoral student in the department of biology at the University of Turku, in Finland.

A horse that spent its entire life with its owner was more likely to allow someone to touch its neck with the toy than a horse that had had several owners during its life. These horses presented more stress behaviors and refused more often to be touched with the toy.

"Horses often have to change ownership, which restricts their ability to make a long-term bond with specific humans. We were particularly interested in studying how the length of the relationship between the horse and the owner affects the horse's behavior in new, potentially stressful situations," she said.

The results showed that horses with shorter relationships with their owner were more reluctant in novel situations and presented more stress behaviors when asked to interact with novel objects and surfaces. On the contrary horses that had at least 6 to 8 years with their owner, were mostly markedly calm when introduced to the surfaces or the stuffed toy.

Horses older than 17 years were more likely to refuse to step on the tarp or the blanket when they were led by a stranger, while they almost all agreed to do it when they were led by their owner.

"Geriatric horses often suffer from poorer eyesight, and it has been shown that they may feel more anxiety toward new situations than younger horses. Therefore, older horses may perceive someone familiar as a secure base, feeling safer to walk over an unknown material when led by a familiar person."

A positive horse-human relationship takes time and is shaped by many factors, including the horse's past interactions with people. "Overall, the results show that animals' relationships with their human caretakers should be better considered in animal welfare and its research," Ms. Liehrmann concluded. **MeV**

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For more information:

Liehrmann O, Viitanen A, Riihonen V, et al. Multiple handlers, several owner changes and short relationship lengths affect horses' responses to novel object tests. *Appl Anim Behav Sci.* 2022;254:105709 doi: 10.1016/j.applanim.2022.105709 https://helda.helsinki.fi/bitstream/handle/10138/347130/1_s2.0_S0168159122001678_main.pdf?sequence=1

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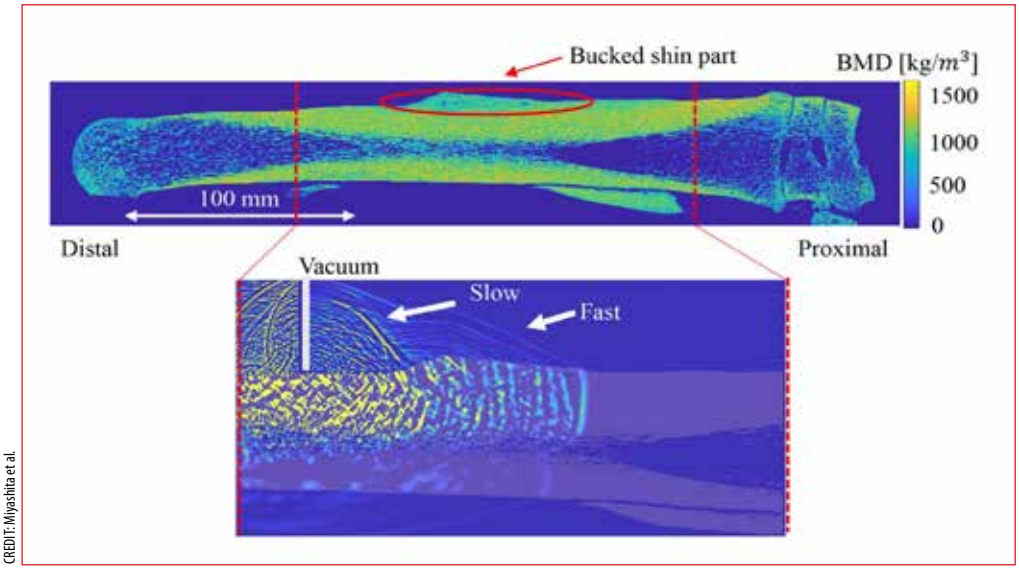
Ultrasonography Could Save Racehorses From Bucked Shins

When racehorses enter training at about 2 years old, they can develop bucked shin—tiny stress fractures and new bone formations in their legs, which occurs in about 70% of the animals, leading to pain and delays in training schedules.

Researchers from Doshisha University, Nagasaki University, and the Japan Racing Association Equine Research Institute developed a method for using ultrasonography to screen for bucked shin.



CREDIT: Miyashita et al.

Top: Cross-sectional view of the bone mineral density distribution in the metacarpal bone measured by computed tomography. Bottom: Simulated wave propagation in bone.

Although radiography can diagnose bucked shin, computed tomography (CT) scans and magnetic resonance imaging are necessary to evaluate the severity of the condition. These strategies are difficult to use on large animals, especially in the field, because horses require anesthesia and must be lying down.

Axial transmission, in which an ultrasound emitter and receiver are placed on the skin to induce and measure wave velocities, is frequently used to study osteoporosis in humans. The method could detect bucked shin more easily and preserve the health and growth of young horses.

"If we can identify this disease at early stages, we can stop training for a period of several weeks or have the horses do light training while they recover," said **Mami Matsukawa**, PhD, an engineering professor at Doshisha University in Kyoto, Japan.

To achieve this task, Dr. Matsukawa and her team created multiple 3D digital models of a racehorse metacarpal bone with varying degrees of bucked shin. Each was based on CT measurements of a real bone with bucked shin.

The researchers simulated ultrasonic wave propagation along the bone model, finding 2 main wave components with different velocities, one faster and one slower. In the area with bucked shin, the fast waves changed speed dramatically because of irregularities in the bone, while the slow waves were almost unaffected.

"We use these velocities of the waves to judge if there is a bucked shin or not," Dr. Matsukawa said. "In an area with bucked shin, there is a new bone formation. If you touch your leg, most likely it is very smooth and there are no irregularities. But if there was some new bone formation, you would find some irregularities in the shape that change the fast wave speed."

The simulations showed that the larger the area of bucked shin, the more variation in the fast waves. Because the axial transmission technique is already established for humans, translating it to work for horses should not be too difficult a task. In comparison to other methods, such ultrasound devices would be small, compact, easy to carry and inexpensive.

While this study used only the velocity as a diagnostic, the team aims to use other wave characteristics, like the modes and attenuation, to obtain material properties of bone in the future. **MeV**

For more information:

Miyashita K, Suzuyama H, Chiba K, et al. Study on ultrasonic wave propagation in equine leg bone for screening bucked shin. *J Acoust Soc Am*. 2022;152(2):890. **https://asa.scitation.org/doi/10.1121/10.0012689**

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References:
[1] Nogradi N, Couetil LL, Messick J, Stochelski MA, Burgess JA. Evaluation of an Omega-3 Fatty Acid Containing Feed Supplement in the Management of Horses with Chronic Lower Airway Inflammatory Diseases. J Vet Intern Med 2015; 29:299-306.
[2] Couetil LL, Cardwell J.M, Gerber V, Lavoie J.-P, Leguillette R, Richard E.A. Inflammatory Airway Disease of Horses. ACVIM Consensus Statement J of Vet Intern Med 2016; 30:503-515 p. 508-510.

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Poor Performance: Could Chemistry Show the Way?

By Paul Basilio

Poor performance is a common cause for concern in racehorses, and the cause can be anything from an occult medical disease to a lack of fitness or just a bad outing, according to **Thomas J. Divers,** DVM, DACVIM, DACVECC, professor at the Cornell University College of Veterinary Medicine.

Dr. Divers emphasized that a thorough history and a complete clinical examination should always be the initial diagnostic step. Serum chemistry analysis should be part of the diagnostic workup when history and clinical examination do not support or reveal a cause of the clinical findings.

If a cause cannot be identified after obtaining a thorough history that includes a review of racing records and a thorough physical examination that includes auscultation and ultrasound examination of both sides of the chest, then the root of the problem may sometimes be detected by examining the horse's serum chemistry values.

"The most common chemistries that can give us a clue as to what's causing poor performance are aspartate aminotransferase [AST], creatine kinase [CK], and GGT—gamma glutamyl transferase," said Dr. Divers at the 67th AAEP Convention in Nashville.

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INDICATION BetaVet® (betamethasone sodium phosphate and betamethasone acetate injectable suspension) is indicated for the control of pain and inflammation associated with osteoarthritis in horses. **IMPORTANT SAFETY INFORMATION** For **Intra-articular** (I.A.) use in Horses. **CONTRAINDICATIONS** BetaVet® is contraindicated in horses with hypersensitivity to betamethasone. Intra-articular injection of corticosteroids for local effect is contraindicated in the presence of septic arthritis. **WARNINGS:** Do not use in horses intended for human consumption. Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis. Additionally, corticosteroids administered to dogs, rabbits and rodents during pregnancy have resulted in congenital anomalies. Before use of corticosteroids in pregnant animals, the possible benefits should be weighed against potential hazards. **Human Warnings:** Not for use in humans. Keep this and all medications out of the reach of children. **PRECAUTIONS:** Corticosteroids, including BetaVet,® administered intra-articularly are systemically absorbed. Do not use in horses with acute infections. Acute moderate to severe exacerbation of pain, further loss of joint motion, fever, or malaise within several days following intra-articular injection may indicate a septic process. Because of the anti-inflammatory action of corticosteroids, signs of infection in the treated joint may be masked. Due to the potential for exacerbation of clinical signs of laminitis, glucocorticoids should be used with caution in horses with a history of laminitis, or horses otherwise at a higher risk for laminitis. Use with caution in horses with chronic nephritis, equine pituitary pars intermedia dysfunction (PPID), and congestive heart failure. Concurrent use of other anti-inflammatory drugs, should be approached with caution. Consider appropriate wash out times prior to administering additional NSAIDs or corticosteroids. **ADVERSE REACTIONS:** Adverse reactions reported during a field study of 239 horses of various breeds which had been administered either BetaVet® (n=119) or a saline control (n=120) at five percent (5%) and above were: acute joint effusion and/or local injection site swelling (within 2 days of injection), 15% BetaVet® and 13% saline control; increased lameness (within the first 5 days), 6.7% BetaVet® and 8.3% saline control; loose stool, 5.9% BetaVet® and 8.3% saline control; increased heat in joint, 2.5% BetaVet® and 5% saline control; and depression, 5.9% BetaVet® and 1.6% saline control. **SHAKE WELL IMMEDIATELY BEFORE USE.** For additional safety information, please see full prescribing information. **CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.**

References: 1. Trotter GW. Intra-articular corticosteroids. In: McIlwraith CW, Trotter GW, eds. Joint Disease in the Horse. Philadelphia: W.B. Saunders; 1996; 237-256.

BetaVet®
betamethasone sodium phosphate and betamethasone acetate injectable suspension

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BetaVet®

betamethasone sodium phosphate &
betamethasone acetate

INJECTABLE SUSPENSION

BRIEF SUMMARY OF PRESCRIBING INFORMATION
(Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension) 6 mg betamethasone per mL
For Intra-Articular (I.A.) Use in Horses

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

INDICATION: BetaVet® is indicated for the control of pain and inflammation associated with osteoarthritis in horses.

DOSAGE AND ADMINISTRATION: Shake well immediately before use.

CONTRAINDICATIONS: BetaVet® is contraindicated in horses with hypersensitivity to betamethasone. Intra-articular injection of corticosteroids for local effect is contraindicated in the presence of septic arthritis.

WARNINGS: Do not use in horses intended for human consumption.
Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis. Additionally, corticosteroids administered to dogs, rabbits and rodents during pregnancy have resulted in cleft palate in offspring. Corticosteroids administered to dogs during pregnancy have also resulted in other congenital anomalies including deformed forelegs, phocomelia and anasarca. Therefore, before use of corticosteroids in pregnant animals, the possible benefits to the pregnant animal should be weighed against potential hazards to its developing embryo or fetus. **Human Warnings:** Not for use in humans. For use in animals only. Keep this and all medications out of the reach of children. Consult a physician in the case of accidental human exposure.

PRECAUTIONS: Corticosteroids, including BetaVet®, administered intra-articularly are systemically absorbed. Do not use in horses with acute infections. Acute moderate to severe exacerbation of pain, further loss of joint motion, fever, or malaise within several days following intra-articular injection may indicate a septic process. Because of the anti-inflammatory action of corticosteroids, signs of infection in the treated joint may be masked. Appropriate examination of joint fluid is necessary to exclude a septic process. If a bacterial infection is present, appropriate antibacterial therapy should be instituted immediately. Additional doses of corticosteroids should not be administered until joint sepsis has been definitively ruled out. Due to the potential for exacerbation of clinical signs of laminitis, glucocorticoids should be used with caution in horses with a history of laminitis, or horses otherwise at a higher risk for laminitis. Use with caution in horses with chronic nephritis, equine pituitary pars intermedia dysfunction (PPID), and congestive heart failure. Concurrent use of other anti-inflammatory drugs, such as NSAIDs or other corticosteroids, should be approached with caution. Due to the potential for systemic exposure, concomitant use of NSAIDs and corticosteroids may increase the risk of gastrointestinal, renal, and other toxicity. Consider appropriate wash out times prior to administering additional NSAIDs or corticosteroids.

ADVERSE REACTIONS: Adverse reactions reported during a field study of 239 horses of various breeds which had been administered either BetaVet® (n=119) or a saline control (n=120) were: acute joint effusion and/or local injection site swelling (within 2 days of injection), 15% BetaVet® and 13% saline control; increased lameness (within the first 5 days), 6.7% BetaVet® and 8.3% saline control; loose stool, 5.9% BetaVet® and 8.3% saline control; increased heat in joint, 2.5% BetaVet® and 5% saline control; depression, 5.9% BetaVet® and 1.6% saline control; agitation/anxiety, 4.2% BetaVet® and 2.5% saline control; delayed swelling of treated joint (5 or more days after injection), 2.5% BetaVet® and 3.3% saline control; inappetance, 3.4% BetaVet® and 2.5% saline control; dry stool, 1.7% BetaVet® and 0% saline control; excessive sweating, 0.8% BetaVet® and 0% saline control; acute non-weight bearing lameness, 0.8% BetaVet®and 0% saline control; and laminitis, 0.8% BetaVet® and 0% saline control.

CLINICAL PHARMACOLOGY: Betamethasone is a potent glucocorticoid steroid with anti-inflammatory and immunosuppressive properties. Depending upon their physico-chemical properties, drugs administered intra-articularly may enter the general circulation because the synovial joint cavity is in direct equilibrium with the surrounding blood supply. After the intra-articular administration of 9 mg BetaVet® in horses, there were quantifiable concentrations of betamethasone (above 1.0 ng/mL) in the plasma.

EFFECTIVENESS: A negative control, randomized, masked field study provided data to evaluate the effectiveness of BetaVet® administered at 1.5 mL (9 mg betamethasone) once intra-articularly for the control of pain and inflammation associated with osteoarthritis in horses. Clinical success was defined as improvement in one lameness grade according to the AAEP lameness scoring system on Day 5 following treatment. The success rate for horses in the BetaVet® group was statistically significantly different (p=0.0061) than that in the saline group, with success rates of 75.73% and 52.52%, respectively (back-transformed from the logistic regression).

ANIMAL SAFETY: A 3-week target animal safety (TAS) study was conducted to evaluate the safety of BetaVet® in mature, healthy horses. Treatment groups included a control (isotonic saline at a volume equivalent to the 4x group); 1X (0.0225 mg betamethasone per pound bodyweight; BetaVet®); 2X (0.045 mg betamethasone per pound bodyweight; BetaVet®) and 4X (0.09 mg betamethasone per pound bodyweight; BetaVet®). Treatments were administered by intra-articular injection into the left middle carpal joint once every 5-days for 3 treatments. Injection site reactions were the most common observations in all treatment groups. Injection site reactions were observed within 1 hour of dosing and included swelling at the injection site, lameness/stiffness of the left front limb, and flexing the left front knee at rest. The injection site reactions ranged from slight swelling (in many horses on multiple days in all treatment groups) to excessive fluid with swelling, pain, and lameness (4x group only). Injection site reactions were observed most commonly on treatment days, and generally decreased in number and severity over subsequent days. The incidence of injection site reactions increased after the second and third injection (number of abnormalities noted on day 10 > day 5 > day 0). In the BetaVet® treated groups the number and severity of the injection site reactions were dose dependent. The 4X BetaVet® group had the highest overall incidence of and severity of injection site reactions, which included heat, swelling, pain, bleeding, and holding the limb up at rest. The control group and 4X group (which received similar injection volumes) had a similar incidence of injection site reactions; however, the severity of reactions was greater in the 4X group. Absolute neutrophils were statistically significantly higher in the BetaVet® treated groups as compared to the control group. Trends toward a decrease in lymphocytes and eosinophils, and an increase in monocytes were identified in the BetaVet® treated groups after the initial dose of BetaVet®. Individual animal values for white blood cells generally remained within the reference range. BetaVet® treated horses also had a trend toward increased blood glucose after the initial dose. Some individual animals showed mild increases in blood glucose above the reference range.

SHAKE WELL BEFORE USING
NADA 141-418, Approved by FDA

For customer care or to obtain product information visit www.betavetequine.com or call 1-800-458-0163.

To report an adverse event please contact American Regent Animal Health at 1-888-354-4857 or email pv@americanregent.com.

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can be caused by liver disease, although it is more commonly the result of muscle disease in racehorses—particularly if there is increased CK activity as well. However, the absence of increased CK activity on a chemistry profile does not rule out muscle disease due to the short half-life of CK.

"CK has such a short half-life," Dr. Divers said. "Unless you draw your sample within 48 hours after the exercise or race, you might miss the increase in CK and be left with just the increase in AST."

Elevated muscle enzyme activity is particularly common in Standardbreds and Thoroughbreds due to recurrent exertional rhabdomyolysis (RER), which has a genetic association. RER is typically intermittent and more common in fillies and excitable horses in training or racing.

"Unless you draw your sample within 48 hours after the exercise or race, you might miss the increase in CK and be left with just the increase in AST."

—Dr. Tom Divers

"The cause of an increase in muscle enzyme activity in the serum of racehorses is probably going to be RER, although there are other sporadic causes of increased muscle enzymes, such as trauma," he said, adding that an increase is rarely due to a selenium deficiency. "I've rarely seen racehorses with myositis that had low blood selenium, and I practice in the Northeast where forage selenium is often low."

Even in the presence of elevated muscle enzymes, there is no guarantee that RER is the culprit for poor performance, as many horses with RER do quite well in their racing careers if they are properly managed by the trainer in consultation with their veterinarian. "If they feed and train the horses properly, RER horses can have successful racing careers," Dr. Divers said.

He added that if a horse appears to be stiff at the end of a race in addition to having elevated muscle enzymes, then RER as a cause of poor performance is likely.

Also, "If muscle enzyme activities are markedly elevated 6 or 12 hours after a poor outing—e.g., CK in the 1000s—and no other cause of the poor performance is found, then RER is likely the cause." he noted. "Regardless, horses with frequent serum elevations in muscle enzyme activity need attention, even if they're winning."

One way to help confirm RER is to have the horse trot for 15 minutes and take a blood sample 3 hours later; If CK is elevated three-fold above baseline values, then RER is likely. There is no available genetic test for the disorder.

GGT

Elevated GGT activity—sometimes called "GGT syndrome"—is another common serum biochemical abnormality in both Thoroughbreds and Standardbreds.

Horses with GGT syndrome typically have serum GGT activities 2- to 5-times higher than the reference range. Other hepatic enzymes, such as SDH and GLDH, will typically be normal or only mildly elevated.

While horses with primary liver disease can have GGT activities in the hundreds or thousands, those with GGT syndrome typically top out around 140 IU/L.

"With GGT syndrome, the increase in serum GGT might be caused by increased production and secretion into serum rather from leakage from damaged liver cells," Dr. Divers said.

With GGT syndrome, GGT activities tend to stay elevated for as long as the horse is maintained in full work. Once the horse is rested, the activities usually return to normal.

So what causes this syndrome?

"I wish I knew," Dr. Divers said. "I had hoped to find out before I retired."

He did explain that finding an increase in serum GGT activity can be assessed similarly to finding an increased serum muscle enzyme activity; normal horses do not have either, but some may still have good race performance.

There is no association between increased GGT syndrome and RER, but "If you examine 10 racehorses with high GGT, you'll likely find 1 or 2 that also have high AST or perhaps high CK activity, but they are almost certainly 2 different diseases," Dr. Divers said.

In young horses that are not fit, serum GGT activity may be increased during training, but those increases usually remain within or only slightly above the reference ranges. Similar to the evaluation of muscle enzyme activity as a determinant of poor performance, there is no magical GGT activity number that confirms the increase as a cause of poor performance.

"Once there is a 3- to 5-fold increase in GGT activity, an effect on performance might be more likely," he said. In addition to poor performance, some

horses with 5-fold increases in GGT activity may have weight loss and dull behavior.

Experimental exercise studies producing elevated GGT syndrome have been conducted in Europe, where they found evidence that the syndrome could be related to maladaptation to heavy training.

In human literature, a mild increase in GGT is identified as a marker of oxidative stress. Dr. Divers said that research teams have found evidence for this in recent horse studies, and the hypothesis is that an increase in serum GGT activity in racehorses could be associated with maladaptation to racing, oxidative stress and increased need to recycle oxidized glutathione into reduced glutathione.

GGT is the most important enzyme in this recycling process. Recent studies have also found that cholestasis may be involved in the syndrome, but this could also be attributed to uncontrolled oxidative stress. If the hypothesis is confirmed, treatments aimed at decreasing oxidative stress and improving bile flow would be recommended.

Dr. Divers did note that if a horse has elevated GGT activity in the presence of other elevated liver enzymes, then testing for the 2 recently discovered equine hepatitis viruses—equine parvovirus-hepatitis and equine hepacivirus—would be indicated.

Other serum chemistries that might suggest a cause for poor performance include elevated globulins (chronic infection), elevated creatinine concentration (renal failure) and abnormal bicarbonate values (high with excessive bicarbonate administration or low with metabolic acidosis).

Dr. Divers mentioned that finding a bilirubin value above the normal reference range in a healthy horse with no other laboratory abnormalities is likely of no concern, as a small number of healthy horses can have indirect (unconjugated) bilirubin values 3 to 4 times the upper range. This is likely a result of a familial deficiency in hepatic uridine diphosphate-glucuronyl transferase activity.

Dr. Divers mentioned that several factors must always be considered when interpreting serum chemistry results:

- The timing of the sample in relation to exercise
- Any unusual delay that may have occurred in testing the sample
- Adverse storage conditions prior to testing.

Also, consider that on rare occasion laboratory results could be erroneous due to laboratory error. If the results do not fit the patient, then retest. **MeV**

16th Century Horse Specimen Identified From the Americas

A newly identified 16th century horse specimen is among the oldest domestic horses from the Americas known to date, and its DNA helps clarify the history of horses in the Western Hemisphere, according to Nicolas Delsol of the University of Florida, and colleagues.

Domestic horses were first brought to the Americas by Europeans in the late 15th century, and they became a pivotal part of European industry and military in the Western Hemisphere. Historical documents suggest the earliest domestic horses were brought to the Caribbean from the Iberian Peninsula, but little archaeological evidence exists to corroborate this. In this study, researchers present a genetic analysis of a late 16th century horse specimen, shedding light on the origins and spread of American domestic horses.

The researchers sequenced the mitochondrial genome from a tooth fragment, originally misidentified as cow, from a Spanish colonial site in what is now Haiti. This is the earliest known complete mitogenome of a post-Columbian domestic horse in the Americas.

This horse belongs to a genetic lineage called equine haplogroup A, whose members are well known from Southern Europe, supporting the idea that they originated on the Iberian Peninsula. This horse's closest living relatives are the feral ponies of Chincoteague Island, Va., which were stranded after a Spanish shipwreck, according to local legend.

Although this study presents only a single mitochondrial genome, the results are significant in multiple respects. The horse's position within a common Iberian lineage supports documentation of the Iberian Peninsula as the source of many early American domestic horses, and this information could clarify our understanding of the path horses took as they colonized the Americas. **MeV**

For more information:

Analysis of the earliest complete mtDNA genome of a Caribbean colonial horse (Equus caballus) from 16th-century Haiti Delsol N, et al. *PLOS ONE.* 2022;17(7):e0270600. **https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0270600**

Get the scoop on ***EPM RECOVERY***

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Antiprotozoal Pellets

IMPORTANT SAFETY INFORMATION: Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril. Safe use 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. For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

[1] Hunyadi L, Papich MG, Pusterla N. Pharmacokinetics of a low-dose and DA-labeled dose of diclazuril administered orally as a pelleted top dressing in adult horses. *J of Vet Pharmacology and Therapeutics* (accepted) 2014, doi: 10.111/jvp.12176. The correlation between pharmacokinetic data and clinical effectiveness is unknown

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US-PRA-210600001

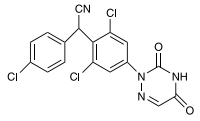
MERCK Animal Health

PROTAZIL®
(1.56% diclazuril)
Antiprotozoal Pellets

FOR ORAL USE IN HORSES ONLY

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #141-268 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)benzeneacetonitrile, has a molecular formula of $C_{17}H_9Cl_3N_4O_2$, a molecular weight of 407.64, and a molecular structure as follows:



Diclazuril is an anticoccidial (antiprotozoal) 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.

DOSAGE 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 weigh 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 2.4-lb bucket of PROTAZIL® will treat one 1274-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).[1] Diclazuril inhibited merozoite production by more than 80% in cultures of *S. neurona* or *S. falcatula* treated with 0.1 ng/mL diclazuril and greater than 95% inhibition of merozoite production (IC_{50}) was observed when infected cultures were treated with 1.0 ng/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 IC_{50} estimates for merozoite production (Dirikolu et al., 1999)[2]. 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 9.6 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, 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 Mayhew neurological scale on Day 48 as follows:

0. Normal, neurological deficits not detected.
1. 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.).
2. Neurological deficit obvious at normal gaits or posture; signs exacerbated with manipulative procedures.
3. Neurological deficit very prominent at normal gaits: horses give the impression they may fall (but do not) and buckle or fall with manipulative procedures.
4. Neurological deficit is profound at normal gait: horse frequently stumbles or trips and may fall at normal gaits or when manipulative procedures were utilized.
5. 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 neurologic 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, 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, biting, 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 (2.27mg/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 2.4-lb (1.1 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., Nattrass, C., Bentz, B. G., Woods, W. E., Carter, W. E., Karpiesiuk, W. G., Jacobs, J., Boyles, J., Harkins, J. D., Granstrom, 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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MERCK Animal Health

"Call of the Wild" Not Better for Horses

Predators, searching for food and water, and even social dynamics increase stress for wild horses.

The danger of predators, the search for food and water, and social dynamics—these could be the elements at the basis of a greater level of stress in free-ranging horses, compared with the ones stabled and under human management, according to study done by Italian researchers.

The researchers examined 47 horses, divided into 3 groups:

1. 16 belonging to the State Police of Ladispoli, where they carried out training and field work;
2. 16 engaged in public order services, in force at the Rome State Police;
3. 15 living in the wild in the mountains of Abruzzo region, recruited thanks to the collaboration of a local breeder.

All the horses were selected based on the absence of acute and chronic pathologies and following the main evaluation parameters of the European Animal Welfare Indicators Project (AWIN) wellness evaluation protocol. The cortisol levels in the horsehair of the selected horses were analyzed.

"Cortisol," said **Francesco Cerasoli,** PhD, the first author of the study, "is a valid indicator of stress, according to scientific literature. So, its amount in the horsehair can be an 'archived,' providing information about the animal's chronic status of well-being."

The results were unexpected, Dr. Cerasoli said. "We saw that the cortisol level was higher in the group of horses living in the wild than in the 2 groups kept in the stable and employed in intense work activities. This evidence contradicts some common beliefs stating that a free-ranging ani mal, capable of expressing its natural behavior would experience higher levels of well-being than the one at work and managed by humans."

It goes without saying, he added, that this would only be true if the management was humane. In other words, the stress factors induced by adequate human management have a lesser impact than those present in the wild.

"Our study shows that the animals managed by State Police, although subjected to work and/or public order service, an activity presumably rich in stressful factors, experience lower cortisol levels. Our conclusion is that proper management by humans seems more respectful of horses' well-being than a pure nature condition," he added.

This helps improve the understanding of factors and conditions that contribute to the well-being of not only horses, but maybe other species. "We must highlight how this survey technique, which can also be extended to other species, could be an objective tool for assessing stress, becoming a point of reference for animal welfare, a field sparking growing interest in recent years," said **Nicola D'Alterio,** PhD, the general manager of the Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise "G. Caporale." **MeV**

For more information:

Cerasoli F, Vulpiani MP, Saluti G, et al. Assessment of welfare groups of horses with different management, environments and activities by measuring cortisol in horsehair, using liquid chromatography coupled to hybrid orbitrap high-resolution mass spectrometry. *Animals*. 2022;12(14):1739.
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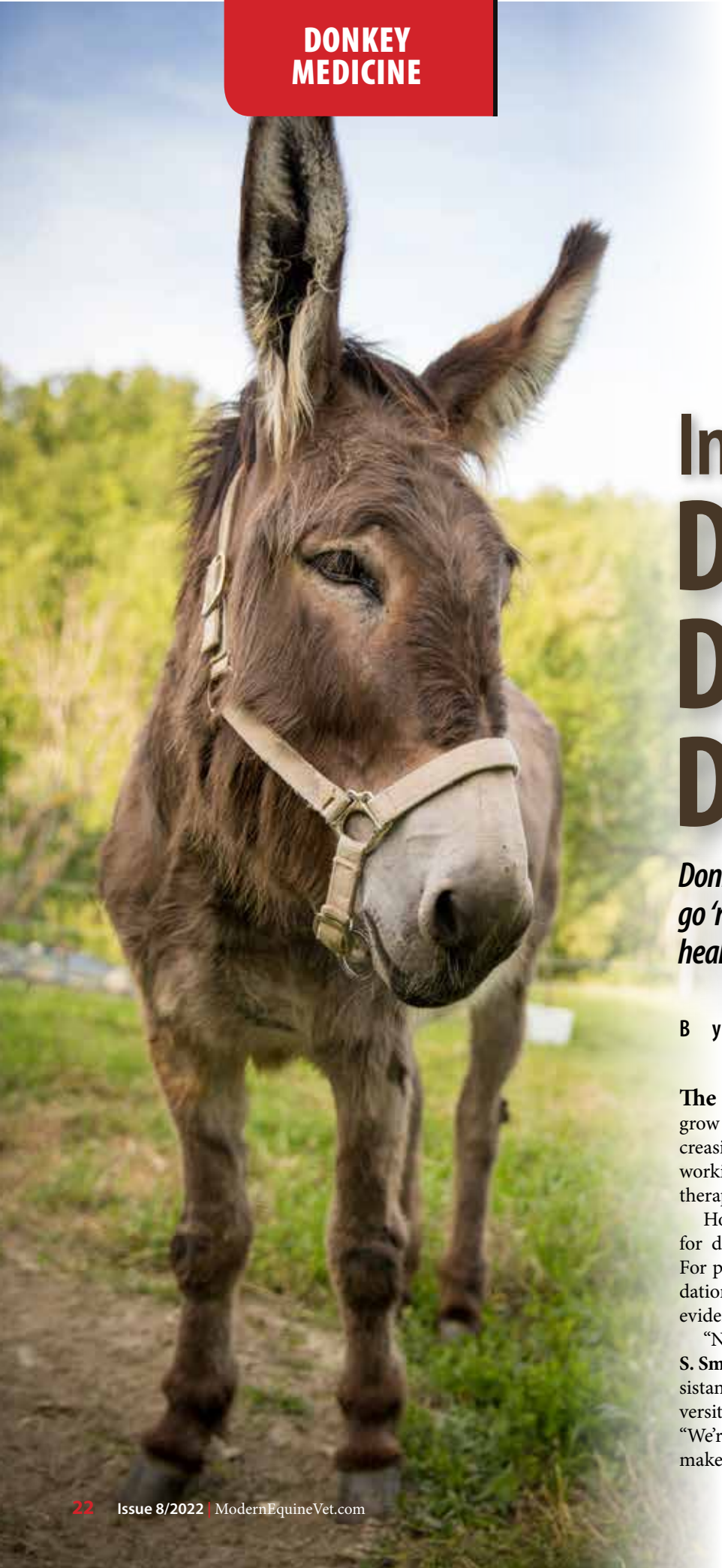

In Search of Drug Data for Donkeys

Donkeys make large parts of the world go 'round, but how do we keep them healthy?

By Paul Basilio

The global donkey population is thought to grow approximately 1% each year, and they are increasingly being recognized as valuable agricultural working animals in addition to their growing role as therapy or companion animals.

However, there are still no FDA-approved drugs for donkeys, and pharmacologic data are lacking. For practitioners who treat donkeys that require sedation, the reason behind the search for accurate, evidence-based dosing data is clear.

"No one wants to get kicked by a donkey," said **Joe S. Smith,** DVM, MPS, PhD, DACVIM, DACVCP, assistant professor of farm animal medicine at the University of Tennessee College of Veterinary Medicine. "We're always looking for sedation strategies that make working with this species a little bit safer."

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Currently, 1 of the prevalent sedation strategies for donkeys is to extrapolate from horses, increase the dose, and hope it works out. It's not ideal, which is why Dr. Smith and colleagues conducted a study examining the pharmacokinetic and pharmacodynamic effects of butorphanol in donkeys.

The study

Eight healthy jacks owned by Ross University were enrolled in a randomized, crossover trial where they were administered IV butorphanol 0.1 mg/kg via jugular catheter, followed by IM butorphanol after a 7-day washout period between treatments.

"We had an intensive blood sampling schedule that was focused on the first 24 hours after IV administration, with the majority of the sampling done within the first 2 hours after administration," Dr. Smith said during a presentation at the 67th AAEP Convention in Nashville. "For IM administration, we extended [sampling] out to 48 hours, but most of the sampling was focused on the first 2 hours."

Dr. Smith and his team ran into some unexpected complications due to some "handling errors" with the samples thanks to international shipping. As the samples were making their way through Customs, 2 IV samples and 1 IM sample were opened, and their labels were removed.

"We had to exclude [3] samples from the analysis because we did not know which tube was which when we received the package on dry ice," he said.

In addition to blood sampling, physiobehavioral characteristics, such as respiratory rate, heart rate, borborygmi and rectal temperatures, were also collected. Any adverse GI effects were also recorded after administration. Sedation was scored on a 3-point scale.

Results

No adverse effects were noted through the study or for 48 hours after either administration. However, borborygmi were significantly decreased vs baseline at 15, 60, and 120 minutes after IV administration, and at 15, 30, and 60 minutes after IM administration. In the IM group, 1 donkey had a slightly elevated respiratory rate 8 hours after IM administration.

The terminal half-life of butorphanol was approximately 30 minutes for IV and 1 hour for IM administrations.

"Butorphanol was rapidly eliminated after the IV dose," Dr. Smith reported. "We were not able to achieve any detectable concentrations after 2 hours post-administration."

For the IM route, the drug stuck around a while longer—concentrations were detected up to 4 hours after administration. The IV route also achieved a much higher concentration in the blood when compared to IM.

"We have a variety of pharmacokinetic studies in horses for butorphanol," Dr. Smith said, "and the donkeys in our study had a considerably lower drug clearance rate than what's been reported in horses."

While many studies in horses report a butorphanol clearance range at around 600 to 700 mL/kg/hr, the study donkeys had a rate of 378 mL/kg/hr (±235 mL/kg/hr).

Sedation scores were not significantly different from any of the animals' baseline readings.

"Based on the sedation scores observed in this study, a butorphanol dose of 0.1 mg/kg does not appear to achieve an effective plane of sedation for donkeys," he explained. "If we were looking to sedate a donkey, we would not be using butorphanol by itself. It would not give us the characteristic sedation for a therapeutic or diagnostic procedure on its own."

While the number of donkeys involved in the study was small—and compounded by the Customs mishap—most pharmacokinetic studies with 4 to 6 animals are adequate.

The shipping incident also impacted the ability of the study to show bioavailability of butorphanol.

"We needed to compare the area under the curve after IV administration to the area under the curve after an extravascular administration from the same animal," Dr. Smith said. "With the labels removed from those samples, we only had [results from] 5 animals instead of 8."

In those 5 animals, however, the calculated bioavailability was 93%.

"If we're going to administer butorphanol in the field, I imagine that it will be easier to give it to them in the muscle instead of in a vein," he added.

Future work

Dr. Smith said that future studies will likely involve a higher dose of butorphanol and more intensive sampling to determine a reliable bioavailability score, as well as investigating butorphanol for analgesia in donkeys.

"With the role that the donkey has worldwide in an increasing population, we are going to need to know more about the analgesic characteristics of the drugs we're using," he said. "Future studies should also focus on multimodal sedation strategies." **MeV**

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