17th

PROCEEDINGS OF THE 2010

KENTUCKY EQUINE RESEARCH

NUTRITION CONFERENCE

Feeding and Veterinary Management OF THE SPORT HORSE

APRIL 26-27, 2010
Lexington, KY

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3910 Delaney Ferry Road
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The Management of Tying-Up in Sport Horses: Challenges and Successes

STEPHANIE J. VALBERG
University of Minnesota, St. Paul, Minnesota

INTRODUCTION

Tying-up occurs in about 3% of exercising horses and (Cole et al., 2004) in a wide variety of breeds, including draft breeds, Warmbloods, Thoroughbreds, Standardbreds, Arabians, Morgans, Quarter Horses, Appaloosas, Paints, and many more. Terms such as exertional rhabdomyolysis, set fast, azoturia, and Monday morning disease have been used to describe this syndrome. The signs of tying-up are all too familiar to many horse owners.

Classically, tying-up occurs after 15 to 30 minutes of aerobic exercise. Horses lose impulsion, develop a stiff, stilted gait, and may pause and stretch out as if to urinate or paw the ground. If pushed to continue exercise, horses sweat excessively, develop a high respiratory rate, and then upon standing become locked in place, unable to walk forward due to painful muscle contractures largely involving the back and hindquarters. Measuring the degree of elevation of muscle enzymes that leak into the bloodstream (creatine kinase, CK; aspartate transaminase, AST) through damaged muscle cell membranes provides a preliminary diagnosis of tying-up. Many horses recover from tying-up after two weeks of rest and never look back; however, others develop repeated episodes with little exertion. Thus, tying-up can be a very frustrating condition to manage.

Successes in the Diagnosis of Tying-Up

One of the most important inroads into understanding tying-up in horses has been the recognition that while acute signs of muscle pain and cramping are similar among horses, the causes of tying-up are varied. For decades, progress in understanding tying-up was hampered by searching for one specific cause of muscle pain and by the false assumption that tying-up pain was due to a lactic acidosis. In fact, there is no scientific validation that lactic acid accumulates in the muscle of horses with tying-up, and many valid studies that show that lactic acid is not present in high levels in horses with tying-up (MacLeay et al., 1999b, 2000; McKenzie et al., 2003; Ribeiro et al., 2004).

Further progress into determining the causes of tying-up was made when the muscle biopsy technique was adapted for horses. Exercise physiologists in the 1970s and 1980s used a 6 mm-diameter needle inserted through a small $^{1}/_{4}$-inch incision to obtain 200-mg samples of gluteus medius muscle without impacting a horse's performance (Lindholm and Piehl, 1974; Snow and Guy, 1976). Samples were not fixed in formalin but frozen immediately in liquid nitrogen to preserve the exact metabolic milieu present at the time samples were obtained. Not only did this technique lead to a comprehensive understanding of the cellular structure and biochemical composition of healthy equine muscle, it also served as a basis to define abnormal cellular appearance and metabolism in tying-up horses. With this

solid comparative base, samples from horses with tying-up from a variety of breeds and fitness levels were studied under controlled research conditions as well as in the field to define specific causes for the clinical syndrome. It became apparent that horses with sporadic episodes of tying-up had no underlying histology or metabolic abnormality in their muscles, whereas many horses with chronic cases had characteristic histological or contractile features that led to the discovery of polysaccharide storage myopathy, recurrent exertional rhabdomyolysis, and malignant hyperthermia.

The incorporation of the muscle biopsy technique into clinical practice over the past 20 years has served not only to enhance the accuracy of diagnosis of muscle disease for individual horses but also to further research into muscle diseases in horses. The repository of over 3,000 muscle and DNA samples from across North America at the Neuromuscular Diagnostic Laboratory, University of Minnesota, has proved to be invaluable in further defining the histological, clinical, epidemiological, pathological, and genetic basis for specific muscle disorders in horses.

As equine genome mapping techniques progress, DNA-based tests are increasingly becoming a part of the diagnostic approach to muscle disease in horses. There are currently four DNA-based tests for muscle disorders in horses, and research is underway to identify more. DNA testing for hyperkalemic periodic paralysis (HYPP), glycogen branching enzyme deficiency (GBED), malignant hyperthermia (MH), and type 1 polysaccharide storage myopathy (PSSM1) are all available. Tests derived from hair roots or blood samples provide a less invasive and more accurate diagnosis than histological interpretation of a muscle biopsy. Studies have now defined the breeds affected with these disorders and in many cases the prevalence of the disorders within breeds. The future may hold the development of panels of tests that could simultaneously screen for all of these disorders in one sample. A full discussion of the heritable basis for exertional muscle disorders in horses is provided in a companion paper by the same author within these proceedings.

The advances in establishing an accurate diagnosis for the cause of tying-up are invaluable because an accurate diagnosis:

(1) defines the likelihood of recurrence of the condition,
(2) establishes reasonable expectations for the horse,
(3) provides for the appropriate selection of targeted dietary therapy and exercise regimes,
(4) determines the likelihood that the horse will pass on the disorder to potential offspring.

Classification of Tying-Up

Some horses develop sporadic exertional muscle damage as a result of nutritional or environmental factors. These sporadic cases of tying-up are usually amenable to treatment once the extrinsic cause of muscle damage is identified. Some horses, however, develop chronic tying-up, and many of these cases are due to an intrinsic and inherited dysfunction of muscle metabolism or muscle contraction.

Sporadic tying-up

The most common cause of sporadic exertional rhabdomyolysis is exercise that exceeds the horse's underlying state of training. Horses that are advanced too quickly in their training, horses that are only ridden sporadically while continually being fed full rations, and horses performing strenuous exercise such as racing or endurance riding without sufficient conditioning commonly develop rhabdomyolysis. In addition, rhabdomyolysis may be more common in horses exercising during an outbreak of respiratory disease. Both equine herpes virus 1 and equine influenza virus have been implicated as causative agents (Harris, 1990; Freestone and Carlson, 1991).

Dietary imbalance. Horses consuming a high-grain diet appear to be more likely to develop tying-up than horses fed a low-grain or fat-supplemented diet. The grain itself may not be responsible for rhabdomyolysis; however, high starch intake may trigger rhabdomyolysis in horses with particular myopathies such as RER and PSSM.

Electrolyte depletion in horses can occur due to dietary deficiency and losses in sweat with strenuous exercise. Sodium, potassium, magnesium, and calcium play key roles in muscle fiber contractility. With severe acute electrolyte depletion such as that found following endurance exercise, serum electrolytes may be below normal ranges (Carlson, 1985). With chronic dietary depletion, however, serum concentrations may not reflect total body electrolyte imbalances.

Selenium and vitamin E. Another postulated cause of sporadic tying-up is the increased generation of free radicals from oxidative metabolism associated with exercise. Selenium, acting via the enzyme glutathione peroxidase, and vitamin E, acting within the lipid component of cell membranes, scavenge free radicals and prevent lipid peroxidation of cell membranes. Primary selenium deficiency is common in young animals living in areas with selenium-deficient soil; however, it has rarely been demonstrated as a cause of exertional rhabdomyolysis (Roneus and Hakkarainen, 1985). In fact, many racehorses with chronic tying-up have higher concentrations of selenium and vitamin E due to zealous dietary supplementation by the trainer. Adequate values for blood selenium are >0.07 mcg/ml. It is not known whether horses that experience repeated episodes of tying-up may generate more free radicals than normal horses. Low vitamin E in the diet is becoming a more common occurrence in many horses with restricted pasture access. Horses with low serum vitamin E may present with muscle soreness, muscle tremors, muscle weakness, and loss of muscle mass. In early stages this may be due to a reversible muscular process. After years of deficiency, oxidative damage to motor nerves can result in permanent damage typical of equine motor neuron disease (Divers et al., 1994). Adequate published values for serum vitamin E are >2.0 mcg/ml. While this may not be difficult to attain with supplementation in some horses, it can be difficult to attain this serum concentrations in certain individuals and much higher daily vitamin E concentrations are necessary.

Chronic tying-up

There are now four specific causes of chronic tying-up that have been recognized, though there are likely many more underlying causes yet to be recognized. These include recurrent exertional rhabdomyolysis, polysaccharide storage myopathy type 1 and type 2, and malignant hyperthermia.

Recurrent exertional rhabdomyolysis (RER). About 5-10% of Thoroughbred racehorses develop tying-up during a racing season, and 75% of these horses have more than four episodes in four months (MacLeay et al., 1999a). Approximately 6% of National Hunt horses (Upjohn et al., 2005) and 13% of polo horses develop tying-up (McGowan et al., 2002b). Horses with a nervous disposition, especially fillies, are highly predisposed. Research studies suggest that a subset of Thoroughbred horses with chronic tying-up have a specific form denoted as RER (Lentz et al., 1999, 2002; Valberg et al., 1999). RER appears to be an inherited, intermittent, stress-induced defect in the regulation of muscle contraction (Lentz et al., 1999, 2002). A breeding trial using Thoroughbred horses with RER confirmed that the characteristic abnormality in muscle contracture is inherited (Dranchak et al., 2005). Recurrent episodes of rhabdomyolysis in Standardbreds and Arabian horses may be due to a similar abnormality, but this has not been confirmed. A heritable basis for RER in Standardbreds was supported by equine lymphocyte antigen profiles in affected horses (Collinder et al., 1997).

The specific defect that causes RER has yet to be identified; however, research suggests it lies within the process of muscle contraction and relaxation. Studies of isolated bundles of muscle cells from RER-affected horses show that RER muscle has abnormal sensitivity to developing contractures when exposed to agents that trigger calcium release from storage sites within muscle cells (sarcoplasmic reticulum) (Lentz et al., 1999, 2002). There are physiological similarities between the contracture results of RER and malignant hyperthermia, yet biochemical and genetic studies do not support an identical biochemical basis for malignant hyperthermia and RER (Ward et al., 2000; Dranchek et al., 2005, 2006). Currently, whole genome association analyses are underway to identify the genetic basis for RER in Thoroughbred horses. Tying-up in susceptible horses is affected by gender, temperament, excitement, stress, dietary starch, exercise duration/intensity, season, and lameness. Females are most commonly afflicted with RER (67% female; 33% male), particularly those that are two years of age and in race training (MacLeay et al., 1999a; McGowan et al., 2002a). Nervous horses are five times more likely to develop RER, and horses with lameness are four times more likely to develop RER. Many owners report that episodes of rhabdomyolysis occur most commonly during estrus, but in one study of racehorses no direct correlation was shown between progesterone fluctuations and serum CK activity (Fraunfelder et al., 1986; Harris et al., 1990) . It is likely that the estrus cycle is one of many factors that combine to trigger tying-up in susceptible horses. Many racetrack practitioners report that the incidence of RER declines when susceptible mares are treated with testosterone.

Susceptible horses receiving more than 5 kg of concentrate feed (oats, corn, molasses mix) are more likely to develop rhabdomyolysis than those receiving 2.5 kg of concentrate feed/day (McKenzie et al., 2003). Dietary effects of high carbohydrate in RER may in part be related to the psychogenic effects of grain on excitability. In horses with RER, glycogen storage does not increase substantially (Valberg et al., 1999). Inclement weather has been cited as a trigger of exertional rhabdomyolysis and rhabdomyolysis

is reported more commonly in the autumn and winter in the United Kingdom (Harris, 1991).

Muscle biopsies from horses with RER that are in training have increased numbers of centrally located nuclei in mature muscle fibers. They may have evidence of varying stages of muscle degeneration and regeneration, and they have normal to slightly increased subsarcolemmal muscle glycogen staining (Valberg et al., 1999). Histopathologic changes are often lacking in horses that have been rested for a period of time prior to biopsy.

Polysaccharide storage myopathy (PSSM). PSSM is characterized by the excessive accumulation of glycogen and an abnormal polysaccharide in skeletal muscle. There are at least two forms of PSSM in horses based on current genetic research.

Type 1 PSSM. Type 1 PSSM is due to an autosomal dominant mutation in the glycogen synthase gene (*GYS1*) which encodes for an enzyme called glycogen synthase (McCue et al., 2009b). The activity of this enzyme appears to be constantly in the "on" position in horses with PSSM, less subject to regulation than in normal horses, and in all horses is enhanced by insulin. Episodes of tying-up in type 1 PSSM appear to result from a deficiency of energy within individual contracting muscle fibers (Annandale et al., 2005). The genetic defect combined with a high-starch diet appears to produce substrate limited muscle oxidative metabolism by both impairing production of acetyl CoA from glycogen (Borgia et al., 2010). Clinical signs of muscle pain in horses with the *GYS1* mutation may be exacerbated by enhanced individual insulin sensitivity (Annandale et al., 2004) as well as by meals that produce elevated blood glucose and insulin levels (Ribeiro et al., 2004).

The distinctive features of type 1 PSSM in muscle biopsy samples are numerous subsarcolemmal vacuoles and dense, crystalline periodic acid Schiff's (PAS) positive, amylase-resistant inclusions in fast-twitch fibers (Valberg et al., 1992; McCue et al., 2009b). A false negative diagnosis of type 1 PSSM by muscle biopsy may occur if biopsy samples are small or if horses are less than one year of age (De La Corte et al., 2002). Genetic testing for the *GYS1* mutation is performed on whole blood or hair root samples at the Veterinary Diagnostic Laboratory at the University of Minnesota (www.vdl.umn.edu/vdl/ourservices/neuromuscular.html).

The *GYS*1 mutation is found in at least 20 different breeds of horses in Europe and North America. Affected breeds include Quarter Horse, Paint, Appaloosa, American Cream, Belgian, Percheron, Gypsy Vanner, Cob Normande, Trekpard, Haflinger, Morgan, Mustang, Rocky Mountain Horse, Tennessee Walking Horse, Hanoverian, Rheinlander, Warmblood horses of unspecified type, and mixed breeds (McCue et al. 2006, 2008a). The prevalence of the PSSM due to the *GYS1* mutation ranges from 8% in Quarter Horses and Paints (McCue and Valberg, 2007; Tryon et al., 2009) to 36% in Belgian draft horses (Firshman et al., 2005), with no reported cases in the Thoroughbreds, Standardbreds, and Arabians tested (McCue et al., 2006).

Type 2 PSSM. Type 2 PSSM refers to horses with excessive muscle glycogen storage that do not have the *GYS1* mutation. The specific cause for type 2 PSSM is not known at present. Type 2 PSSM appears to account for about 25% of PSSM cases in Quarter Horse-related breeds, 80% of PSSM cases in many

Warmblood breeds, and is present in Arabians and Thoroughbreds (McCue et al. 2006, 2008a). The acronyms EPSM and EPSSM have also been used for polysaccharide storage myopathy, although they do not indicate a specific genotype (Valentine, 2002; Valentine and Cooper, 2005). One of the most common presenting complaints in Warmbloods with PSSM is a gait abnormality characterized by lack of impulsion and shifting undiagnosed lameness (Hunt et al., 2008), although classic signs of tying-up and sore muscles may also occur. Type 2 PSSM at present must still be diagnosed by muscle biopsy (McCue et al., 2009a). Muscle biopsies from horses with type 2 PSSM have increased PAS staining for glycogen and aggregates of granular PAS-positive polysaccharide in the cytoplasm or under the sarcolemmal. False positive diagnosis is possible for type 2 PSSM in highly trained horses that normally have higher muscle glycogen concentrations or in formalin-fixed sections that show a greater deposition of subsarcolemmal glycogen in healthy horses.

Malignant hyperthermia (MH). Malignant hyperthermia is due to an autosomal dominant mutation in the skeletal muscle ryanodine receptor and is present in 1% or less of Quarter Horses (Aleman et al., 2004, 2009). Affected horses may intermittently show signs of tying-up and high body temperatures (Aleman et al., 2009) Some MH-affected horses have died suddenly after an episode of tying-up. The MH defect can coexist with the *GYS1* mutation for type 1 PSSM (McCue et al., 2008a). The combination of these two mutations makes signs of tying-up more severe, increases recurrence of high serum CK, and makes horses more resistant to improvement with changes in diet and exercise (McCue et al., 2008b). In addition, horses with MH may develop classic signs under general anesthesia of excessive body temperature, rigor, metabolic acidosis, and death (Aleman et al., 2005). Genetic testing is recommended in Quarter Horses and Paints with difficult to manage forms of PSSM or a family history of post-anesthetic complications. Testing is available through the Veterinary Diagnostic Laboratory at the University of Minnesota (www.vdl.umn.edu/vdl/ourservices/neuromuscular.html).

Successes in the Management of Tying-Up

Successful strategies to manage tying-up followed the ability to accurately diagnose the cause of tying-up in individual horses. The contributions of changes in gait to muscle soreness, diagnosis and treatment of underlying lameness, and development of equine rehabilitation therapy have all led to faster healing, stronger muscles, full range of joint motion, and a lower rate of recurrence of sporadic muscle injuries. Advances in our understanding of equine exercise physiology and nutrition and controlled research trials have also led to the development of targeted diet and exercise regimens that minimize the development of muscle soreness in chronically afflicted horses.

Sporadic tying-up

For sporadic cases of tying-up, a few weeks of rest in a small paddock after the initial episode and nonsteroidal anti-inflammatory medication form the basis for initial treatment. Once muscle enzymes in the bloodstream return to normal, a horse can gradually resume exercise. Sore muscles in many horses may be secondary to changes in gait or overt lameness arising from hoof balance, ligament, tendon,

bone, or joint pain. In such cases, changes in diet and exercise regimes will be unsuccessful until a long-term holistic approach is taken that combines treatment of orthopedic disorders and rehabilitation therapy in addition to a balanced low-starch diet and a gradually increasing exercise regime. In addition, the degree to which the muscles necessary for a given type of performance are recruited during a fitness program should be evaluated to ensure overexertion does not contribute to tying-up. A new program designed to provide gradually increasing intervals of recruitment of these muscle groups may be necessary. For example, horses competing over cross-country courses should be exposed to intervals of speeds that replicate those attained during competition. Horses competing in dressage need to gradually develop the strength and coordination necessary to perform specific movements and sustained collection.

Chronic tying-up

Rest and turnout. For chronic cases, prolonged rest after an episode appears to be counterproductive and predisposes RER and PSSM horses to further episodes of tying-up. Providing daily turnout with compatible companions can be very beneficial, as it decreases anxiety in RER horses and enhances energy metabolism in PSSM horses. If excitement is a triggering factor for RER, stressful environmental elements should be minimized. Many horses respond to a regular routine including feeding prior to other horses and training first before other horses, especially if the horse becomes impatient while waiting. The use of hot walkers, exercise machines, and swimming pools should be evaluated on an individual basis, as some horses develop tying-up when using this type of equipment. Horses that develop rhabdomyolysis at specific events such as horse shows may need to be reconditioned to decrease the stress level associated with such events. Most PSSM horses are calm and not easily stressed. They do best when turned out on large pastures without lush grass where they move about on a daily basis. Grazing muzzles may be of benefit to PSSM horses for periods when grass is particularly lush.

Exercise. Regular daily exercise is important for managing all forms of tying-up and days off should be minimized. Following chronic episodes of tying-up in Thoroughbreds and Standardbreds, mild, calm low-intensity daily exercise (<15 minutes) or preferably extensive daily turnout is recommended until serum CK is less than 1,500 U/L. Thoroughbred racehorses often develop tying-up when riders fight to keep horses at a slower speed (gallop exercise), and therefore this should be avoided (MacLeay et al., 1999a). Standardbreds often develop ER after 15-30 minutes of submaximal jogging. Interval training and reduction of jog miles to no more than 15 minutes per session are recommended (Valberg et al., 1993). For riding horses with RER, a prolonged warm-up with adequate stretching is recommended. Rest periods that allow horses to relax and stretch their muscles between 2-5 minutes periods of collection under saddle may be of benefit. Event horses may require training that incorporates calm exposure to speed work to prevent rhabdomyolysis, as well as interval training at the speeds achieved during competitions.

Reintroduction of exercise to PSSM horses needs to be more gradual than approaches used for RER. Important principles include: (1) providing adequate time for adaptation to a new diet prior to commencing exercise; (2) recognizing that the duration of exercise is more important to restrict than the intensity of exercise; (3) ensuring the exercise is gradually introduced and consistently performed; and (4) minimizing any days without some form of exercise.

Dietary management. A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals is the core element of treating all forms of tying-up. As with any horse, forage is recommended at a rate of 1.5-2% of body weight. In general, grass hay is preferable to alfalfa hay. Diets with a restricted amount of starch and sugar and supplemental calories supplied with fat are the basis for dietary management. For Thoroughbreds and Standardbreds with RER, the challenge is supplying an adequate amount of calories in a highly palatable feed to meet their daily energy demands. Out of the total daily calories required, it is recommended that less than 20% digestible energy (DE) be supplied by starch and at least 15% be supplied by fat. Controlled experimental studies using Thoroughbreds with RER show that serum CK activity is significantly lower when horses are fed a specially formulated high-fat, low-starch feed rather than an isocaloric amount of high-starch grain (MacLeay et al., 2000; McKenzie et al., 2003). Given the close relationship between nervousness and RER, assuaging anxiety and excitability by reducing dietary starch and increasing dietary fat may decrease susceptibility by making these horses calmer prior to exercise. To increase a horse's energy during the race, some race-horse trainers prefer to supplement with a titrated amount of grain three days prior to a race if horses are on a low-starch, high-fat feed.

For PSSM horses, the challenge can be to provide adequate fat for energy metabolism while preventing excessive weight gain. If horses are overweight, reducing caloric intake by using a grazing muzzle, restricting hay to 1.5% of body weight and providing a vitamin/mineral ration balancer are recommended. Adding excessive calories in the form of fat to an obese horse is inadvisable. Until horses are of normal weight, fat metabolism can be enhanced by riding horses after a 5-8 hour fast as a means to elevate plasma free fatty acids. Once a horse has achieved the desired body weight, low-starch and low-sugar feeds combined with dietary fat can be introduced. The starch and sugar content of the diet of PSSM horses needs to be managed more stringently than for RER. Owners report that this type of diet improves clinical signs of muscle pain, stiffness, and exercise tolerance in draft horses, Warmbloods, Quarter Horses, and horses of other breeds with PSSM when combined with the recommended exercise program. Dietary change appears to have lesser impact on alleviating gait changes such as shivers (Hunt et al., 2008). In Quarter Horses with PSSM, providing less than 10% of daily digestible energy as dietary starch and 13% of daily digestible energy as dietary fat during a six-week trial resulted in normal serum CK activity four hours post exercise (Ribeiro et al., 2004). The beneficial effect of the low-starch, high-fat diet used in this study (Re-Leve®) was believed to be the result of less glucose uptake into muscle cells and provision of more plasma free fatty acids for use in muscle fibers during aerobic exercise. Quarter Horses naturally have very little lipid stored within muscle fibers and provision of free fatty acids may overcome the disruption in energy metabolism that appears to occur during aerobic exercise. The addition of fat alone is not beneficial and an exercise program must be instituted for PSSM horses to show clinical improvement. Based on anecdotal experience, some authors recommend that >20% of daily caloric intake be supplied by fat (0.5 kg of fat). There are no controlled studies that support the need to feed every PSSM horse one pound of fat (3 cups or more of oil), and there are controlled studies to show PSSM horses can consume less fat and have normal CK activity (Borgia et al., 2010). In the author's experience, there is a great deal of variation in individual needs for fat supplementation and this should be balanced with the horse's weight.

Several well-balanced, low-starch/high-fat commercial diets are suitable for horses with RER and PSSM. Some commercial feeds meet the recommended nutritional needs of RER and PSSM horses in one pelleted ration and have been thoroughly evaluated (Re-Leve®). These feeds typically contain 10-14% fat by weight and less than 20% starch or nonstructural carbohydrate (NSC) by weight. Some feed companies offer similar nutritional content by blending two or more manufactured feeds or by supplementing with oils or rice bran. Palatability of pelleted feeds is usually higher than feeds containing pour-on oils or loose rice bran. At present, the NSC content of equine feed products is not listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers in designing an appropriate diet. Not all of these feeds are equally effective. Hay with an NSC content of 12% or less is recommended for PSSM horses.

Medication. Tranquilizers may be of value in treating excitable horses prone to RER. Dantrolene sodium is a medication that acts to decrease release of calcium from the calcium release channel in skeletal muscle. When given to RER horses 60 to 90 minutes prior to exercise, dantrolene appears to attenuate muscle damage but is expensive to use on a continuous basis. Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels and has also been used as a therapeutic agent to prevent RER. Some mares appear to exhibit signs of ER during estrus, and it may well be of benefit in these horses to suppress estrus behavior using progesterone injections. Testosterone and anabolic steroids are used at racetracks to prevent signs of RER, but the efficacy has not been evaluated.

To date there are no tested management strategies for horses with MH, although dantrolene seems like a reasonable but expensive approach. Horses with both MH and PSSM have been shown to respond to high-fat, low-starch diets although their response is not as favorable as horses with PSSM alone (McCue et al., 2009b).

Conclusion

Managing muscle disorders in sport horses involves the identification of the specific cause of tying-up, rest, selection of medications (to reduce pain, address deficiencies, or counteract disease mechanisms), diet regimes designed to counteract any metabolic deficiencies, rehabilitation therapy, and gradual reintroduction of exercise up to the intended performance. Many advances have been made over the course of the last 30 years in identifying specific causes for tying-up, developing new diagnostic tests, and researching specific diet and exercise programs to decrease recurrence of muscle pain. The future likely holds identification of new forms of tying-up, development of more genetic tests to diagnose specific causes, and continued evolution of dietary management and exercise regimes tailored to individual cases.

Conflict of interest statement: Drs. Valberg, Mickelson, and McCue own the license for PSSM testing and receive sales income from its use. Their financial and business interests have been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policies.

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