

Exertional Rhabdomyolysis

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Exertional rhabdomyolysis is a syndrome with many causes. Sporadic cases may be caused by overexertion or dietary imbalances, whereas chronic cases may be caused by inherent defects in intracellular calcium regulation (recurrent exertional rhabdomyolysis) or glycogen metabolism (polysaccharide-storage myopathy). Modification of diet and training regimens can decrease the likelihood of recurrence. Author's address: Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue, St. Paul, MN 55108; e-mail: valbe001@umn.edu. © 2006 AAEP.

1. Introduction

Exertional rhabdomyolysis (ER), literally the dissolution of striated muscle with exercise, is an age-old problem in horses. Over the past century, a number of terms have been used to describe this syndrome including tying up, set fast, Monday morning disease, azoturia, chronic intermittent rhabdomyolysis, and equine-rhabdomyolysis syndrome. A great deal of controversy has arisen regarding the cause of this syndrome; however, it has become clear that these terms really incorporate a number of different disease processes that share a common manifestation of muscle pain. The purpose of this paper is to review causes and treatments for various forms of ER.

2. Prevalence and Risk Factors

Approximately 3% of exercising horses are reported to have had an episode of ER in the last 12 mo.¹ The prevalence of ER is higher among racehorses^{2,3} and National Hunt Horses⁴ (~6%); in polo horses, it is as high as 13%.⁵ The development of rhabdomyolysis is influenced by factors such as exercise routines, sex, age, and temperament of the horse as well as diet and presence of lameness.²⁻⁷

3. Clinical Signs

Horses with ER usually show signs of muscle stiffness, shifting hindlimb lameness, elevated respiratory rate, sweating, firm painful hindquarter muscles, and reluctance to move that lasts for several hours. There may be a decrease in the severity of clinical signs as horses get older.^{3,4} Subclinical episodes occur in some horses, causing decreased performance, painful muscles, and reluctance to maintain collection without other overt signs.

4. Diagnosis

A diagnosis of ER is based on clinical signs of muscle stiffness and pain after exercise in conjunction with elevations in serum creatine kinase (CK) and aspartate transaminase (AST) activities. The degree of elevation of these enzymes in serum is dependant on the severity of muscle damage as well as the length of time that has elapsed between the sample collection and the occurrence of muscle damage.⁸ Peak serum values occur ~4–6, 12, and 24 h after myonecrosis for CK, lactate dehydrogenase (LDH), and AST, respectively. Clearance of these enzymes from the bloodstream after rhabdomyolysis occurs rapidly for CK, more slowly for LDH, and is most

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prolonged for AST. Moderate to severe rhabdomyolysis may also produce myoglobinuria detected by urine stick tests as Hb-positive in the absence of hemolysis or red blood cells in the urine.^{8,9}

With severe rhabdomyolysis, electrolyte abnormalities such as hyponatremia, hypochloremia, hypocalcemia, hyperkalemia, and hyperphosphatemia may occur.¹⁰ These derangements result from sweating as well as shifting of fluid and electrolytes (sodium, chloride, and calcium) down a concentration gradient into damaged muscle. Release of electrolytes such as potassium and phosphorus from damaged muscle cells can result in increased serum concentrations. A metabolic alkalosis is the most common acid-base abnormality with ER, because it is a compensation for hypochloremia.¹¹ Lactic acidemia is rarely, if ever, observed.^{11,12} Azotemia may occur in dehydrated horses from myoglobinuric nephrotoxicity.

Establishing that ER is a primary cause of poor performance is challenging when episodes of ER are intermittent. Persistent elevation in AST may indicate previous episodes of ER; however, if serum muscle enzymes are normal, an exercise challenge can be of value to detect underlying subclinical ER.¹³ Blood samples are obtained before exercise and ~4–6 h after exercise to evaluate peak changes in CK activity. Fifteen minutes of easy, uncollected trotting will detect significant, yet subclinical muscle damage in horses prone to ER.¹⁴ This test is selected rather than other maximal exercise tests, because it provides more consistent evidence of subclinical rhabdomyolysis with less risk of overexertion.⁸ If signs of stiffness develop during the test, exercise should be concluded. A three- to four-fold increase from basal CK activity is indicative of subclinical ER.^{13,14} Small fluctuations in serum CK activity may occur with exercise because of enhanced muscle-membrane permeability, particularly if exercise is prolonged or strenuous and the horse is untrained.⁶ However, most normal horses show little change in CK activity with this submaximal test.

5. Classification

As mentioned previously, ER represents a syndrome of muscle pain and necrosis that likely has numerous underlying causes. In practice, it may be useful to initially determine if a horse with ER falls into one of two main categories: (1) horses in which an intrinsic muscle defect does not seem to be present, but a temporary imbalance within the muscle cells does cause sporadic episodes of ER, and (2) horses in which the primary underlying susceptibility seems to be the result of an intrinsic defect in the muscle, sometimes referred to as chronic ER.

Sporadic cases of ER are usually characterized by a history of adequate performance before onset of episodes and a successful return to performance after a reasonable period of rest, provision of a balanced diet, and a gradual training program. Horses with these

sporadic occurrences of ER may be of any age, breed, or sex, and they may be involved in a wide variety of athletic disciplines.^{1,7} A familial history of ER is absent. Episodes of ER may recur over a period of time before resolving. Episodes of sporadic ER seem to be triggered by external perturbations that affect muscle function, and after correction, complete resolution is possible. In many cases, horses are initially presumed to have sporadic ER; however, if episodes of ER recur over time despite the best management, a diagnosis of chronic ER would be more likely.

Horses often develop signs of chronic ER shortly after entering an initial training regimen and with very little prior conditioning. Certain breeds of horses seem to have a higher prevalence of chronic ER,^{1,15} and within these breeds, specific family lines seem particularly predisposed.^{16–18} This has led to the suggestion that there are intrinsic inherited defects in muscle function that may predispose horses to chronic forms of ER. Documented forms of chronic ER include polysaccharide-storage myopathy and recurrent exertional rhabdomyolysis. Most likely, there are other forms of chronic ER that are, at present, unrecognized.

6. Pathogenesis of Sporadic ER

Sporadic cases of ER may develop as a result of exercise beyond training adaptation, injury from repetitive motion, heat exhaustion, or certain dietary imbalances.

Overexertion

A history of an increase in work intensity without a foundation of consistent training for this level of intensity is usually the basis for suspecting a training imbalance as a cause of ER. Signs of muscle stiffness and gait changes may be mild and are accompanied by modest elevations of serum CK activity.¹⁹ Pathological changes are often not evident in light microscopic evaluation of muscle biopsies in horses performing unaccustomed exercise, but electron microscopy shows significant disruption of the alignment of muscle-contractile proteins within muscle fibers.¹⁹

Repetitive overuse of muscles, such as occurs with overtraining, may result in exercise intolerance and is associated with pathologic changes such as increased muscle-fiber size variation and centrally located myonuclei in muscle biopsies.^{13,20,21}

Heat Exhaustion

Heat exhaustion occurs most commonly in horses exercising in hot, humid weather. Signs of heat exhaustion include weakness, ataxia, rapid breathing, muscle fasciculation's, sweating, and collapse. The body temperature may be elevated to 105–108°F. Muscles are frequently not firm on palpation, serum CK activity can be markedly elevated, and myoglobinuria may be noted.²²

Dietary Imbalances

Episodes of ER may be triggered by diets with a high non-structural carbohydrate (NSC) content, inadequate selenium and vitamin E,²³ or electrolyte imbalances.²⁴ Serum vitamin E and either whole-blood selenium concentrations or glutathione-peroxidase activity can be helpful in assessing potential deficiencies. Horses with ER are infrequently deficient in selenium; anecdotal reports suggest that, in some cases, supplementation may prevent further episodes of ER.²⁵

Electrolyte Imbalances

Electrolyte balance within the body is difficult to determine accurately.²⁶ One suggested means to practically assess electrolyte balance in horses is to measure urinary fractional excretion (FE) of electrolytes.²⁴ Measurement of urinary electrolyte excretion as an indicator of electrolyte balance is complicated, because marked variation can occur from diet, exercise, and sampling technique between individuals as well as within individuals from day to day.^{26,27} Furthermore, the high calcium-crystal concentration of alkaline equine urine requires acidification to accurately assess calcium and magnesium content.²⁷ The high potassium content interferes with sodium analysis using conventional ion-specific electrodes. If urinary FE is to be performed, the best results are obtained by using a highly standardized method with gas-chromatography mass-spectrometry analysis rather than by conventional ion-specific electrodes.²⁷

7. Recurrent Exertional Rhabdomyolysis

The term recurrent exertional rhabdomyolysis (RER) is used to describe a subset of ER that is believed to be caused by an abnormality in intracellular calcium regulation.^{13,28,29} Research into RER has primarily been performed in Thoroughbreds and to a lesser extent, Standardbreds.^{28–31} There are undocumented reports of some Arabian horses with ER that may also suffer from this specific form of myopathy.

Prevalence and Risk Factors

The prevalence of RER in Thoroughbred racehorses is remarkably similar around the world: 4.9% in the United States,² 5.4% in Australia,¹ and 6.7% in the United Kingdom.³ Exercise obviously increases the prevalence of RER in horses, and episodes are observed more frequently after horses achieve a level of fitness.^{2,3} The type of exercise seems to be of importance, because episodes of rhabdomyolysis occur most often when horses are restrained to a slower pace during exercise but occur infrequently after racing.² Thoroughbred horses often show evidence of rhabdomyolysis after the steeplechase or at the beginning of the cross-country phase of a three-day event.

Mares more commonly show signs of RER than males; however, no general correlation has been ob-

served between episodes of rhabdomyolysis and stages of the estrus cycle. There seems to be an interaction between age and gender in RER horses such that the proportion of affected females to males is much higher in young horses compared with older age groups. Temperament exhibits a strong effect on the expression of RER; nervous horses having a significantly higher incidence of rhabdomyolysis than calm horses. Young fillies are more likely to have a nervous temperament than mares or male horses. Horses on a high grain diet are more likely to show signs of RER, and one study found a higher prevalence of rhabdomyolysis among horses with various lamenesses.²

Genetics

A genetic susceptibility to RER seems to exist in Thoroughbred horses. Studies of RER-afflicted horses have shown that affected horses may pass the trait along to 50% or more of their offspring.^{16,17} A breeding trial conducted at the University of Minnesota as well as pedigree studies from a variety of farms, suggest that susceptibility to RER is inherited as an autosomal dominant trait.^{16,17} Studies of allelic frequencies of genetic markers in Standardbred horses with RER were significantly different from healthy Standardbred horses, suggesting that there is potentially a heritable basis for this condition in this breed as well.³² There are anecdotal reports of higher prevalence of RER in certain Arabian horse families.

Diagnosis

In practice, many trainers evaluated serum CK or AST activities to identify horses with reduced performance because of subclinical episodes of RER. A number of factors may affect muscle-enzyme elevations in serum. Reliability can be improved if blood samples are obtained at a standardized time, preferably 4–6 h after exercise (when CK peaks), and consistently with regard to exercise on the preceding day, because serum CK activity is higher on exercise days that are preceded by a day or more of rest.^{6,33,34} In addition, normal values need to be adjusted for the age and sex of horses. Two-year-old fillies generally show greater fluctuations in serum CK activity during race training than 3-yr-old fillies or geldings.^{6,34}

A presumptive diagnosis of RER is based on clinical signs of muscle pain and the presence of risk factors commonly associated with RER. Skeletal-muscle biopsies from Thoroughbred and Standardbred horses with active signs of RER often show an increased number of mature muscle fibers with centrally displaced nuclei, increased subsarcolemmal staining for glycogen, and variable amounts of muscle necrosis and regeneration (Fig. 1).^{8,13} There is a notable absence of abnormal amylase-resistant polysaccharide in muscle biopsies from RER horses.¹³ Research is currently underway to identify a genetic

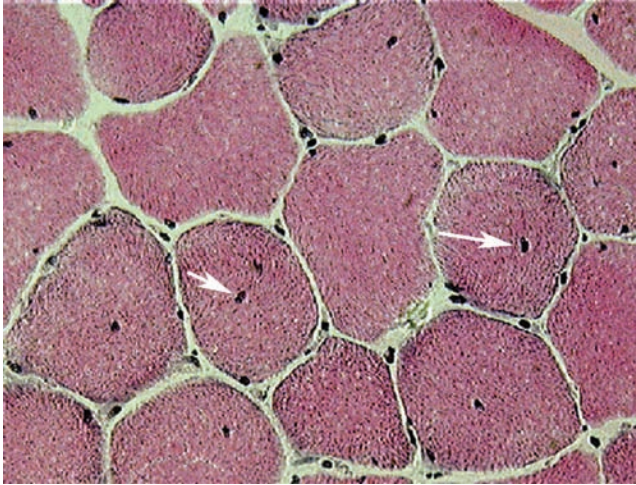


Fig. 1. Hematoxylin and eosin stain of a cross-section of gluteal muscle from a Thoroughbred with recurrent exertional rhabdomyolysis. Note the presence of numerous centrally displaced myonuclei (arrows).

marker that would help to identify horses susceptible to this genetic disease.¹⁶

Pathogenesis

Several studies have clearly shown the rhabdomyolysis is not caused by lactic acidosis.^{12,33,35} More recent research suggests that horses with RER may inherit an abnormality in intramuscular calcium regulation that is intermittently manifested during exercise.^{28,29} An abnormality in the regulation of muscle-cell contraction in Thoroughbred and Standardbred horses with RER was first suggested by Beech et al.^{30,31} from studies of semitendinosus muscles.^{30,31} Further studies of intact intercostal muscles from Thoroughbred horses with RER found an abnormal sensitivity to the development of muscle contracture on exposure to potassium, caffeine, and halothane in RER compared with normal horses.²⁹ Calcium imaging of myotubes derived from RER horses also showed enhanced calcium release in response to caffeine.²⁸

Other studies found increased myoplasmic calcium concentrations in intercostal muscle obtained from horses with rhabdomyolysis.³⁶ The abnormal contracture responses of RER horses do not seem to be caused by increased sensitivity of myofilaments from RER horses to Ca^{2+} .³⁷ The characteristics of RER muscle are very similar to those of humans and swine with malignant hyperthermia; however, studies of isolated sarcoplasmic-reticulum membrane vesicles from RER horses failed to identify the typical abnormalities in the ryanodine receptor seen with malignant hyperthermia.³⁸ Thus, at present, the exact defect in intracellular calcium regulation with RER is not known.

8. Treatment of ER

Treatment of ER is directed at relieving anxiety and muscle pain and replacing fluid and electrolyte

losses. Tranquilizers such as acepromazine (0.04–0.07 mg/kg), xylazine (0.2–0.5 mg/kg), or detomidine (0.02–0.04 mcg/kg) combined with butorphanol (0.01–0.04 mg/kg) provide excellent sedation and analgesia. For horses with extreme pain and distress, a constant-rate infusion of detomidine, lidocaine, or butorphanol may provide additional pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen (2.2 mg/kg), phenylbutazone (2.2–4.4 mg/kg), or flunixin meglumine (1.1 mg/kg) are frequently used to relieve pain but should be used with caution in dehydrated animals. IV or intragastric dimethyl sulfoxide (as a <20% solution) is used as an antioxidant, anti-inflammatory, and osmotic diuretic for severely affected horses. Methyl prednisolone succinate (2–4 mg/kg, IV) has been advocated by some veterinarians in the acute stage if horses are recumbent. Muscle relaxants such as methocarbamol (5–22 mg/kg, IV, slowly) seem to produce variable results possibly depending on the dosage used. The administration of dantrium sodium (2–4 mg/kg, orally) in severely affected horses may decrease muscle contractures and possibly prevent further muscle necrosis. The dose can be repeated every 4–6 h if necessary, and best absorption occurs when given after at least 3 h of fasting. Overdosing produces muscle weakness.

Severe rhabdomyolysis can lead to renal compromise because of the ischemic and combined nephrotoxic effects of myoglobinuria, dehydration, and NSAIDs. In mildly dehydrated horses, provision of free-choice electrolytes and water or administration of fluids through a nasogastric tube may be adequate. Horses with moderate to severe dehydration require IV administration of balanced polyionic-electrolyte solutions. Hyperkalemia can occur with severe rhabdomyolysis, necessitating the use of isotonic sodium chloride. If hypocalcaemia is present, supplementation with IV fluids of 100–200 ml of 24% calcium borogluconate is recommended, but serum calcium should not exceed a low normal range. Affected animals are usually alkalotic, making bicarbonate therapy inappropriate. In severely affected animals, regular monitoring of serum creatinine is advised to assess the extent of renal damage.

Horses should be stall rested on a hay diet for a few days. Small-paddock turnout in a quiet area for a few hours twice a day is helpful. Horses may be hand walked at this time, but not for >5–10 min at a time. For horses with sporadic forms of tying up, rest with regular access to a paddock should continue until serum muscle-enzyme concentrations are normal. For chronic cases of tying up, this much rest may not be appropriate. Training should be resumed gradually, and a regular exercise schedule that matches the degree of exertion to the horse's underlying state of training should be established.

9. Management of ER

Environment

If one of the main triggering factors for ER seems to be excitement, finding ways to reduce stress is recommended to help decrease episodes of rhabdomyolysis in susceptible horses. Many horses respond to a regular routine including feeding first before other horses and training first before other horses, especially if the horse becomes impatient while waiting. Other ways to decrease excitement include housing in an area of the barn where horses are not always walking past and next to calm, companionable horses. The use of hot walkers, exercise machines, and swimming pools should be evaluated on an individual basis because some horses develop rhabdomyolysis 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. Providing daily turnout with compatible companions can be very beneficial for RER horses, and it may decrease anxiety and thereby, the likelihood of rhabdomyolysis.

Exercise

Many horses with mild episodes of tying up are best turned out for a few days and then returned gradually to regular daily exercise. Horses with more severe damage may require additional time off before gradually resuming exercise. When back in training, it is recommended to avoid days off of exercise, because serum CK activity is higher when horses are exercised after a day of rest. A prolonged warm-up with adequate stretching is believed to decrease episodes of rhabdomyolysis. Rest periods that allow horses to relax and stretch their muscles between periods of collection under saddle may be of benefit. Event horses may require training that incorporates calm exposure to steeplechase as well as interval training at the speeds achieved during the steeplechase to prevent rhabdomyolysis during competitions. Thoroughbred racehorses often develop rhabdomyolysis when riders fight to keep horses at a slower speed, and therefore, this should be avoided. Standardbred horses often develop rhabdomyolysis after 15–30 min of submaximal trotting,⁸ and therefore, interval training and reduction of jog miles to no more than 15 min per session is recommended.

Medications

Low doses of tranquilizers, such as acepromazine, before exercise have been used in RER horses prone to excitement. A dose of 7 mg (IV) 20 min before exercise is reported to make horses more relaxed and manageable.³⁹ Reserpine and fluphenazine, which have a longer duration of effect, have also been used for this purpose.⁴⁰ Horses given fluphenazine may occasionally exhibit bizarre behavior. Use of tranquilizers may only be necessary

when horses are in their initial phase of training and accommodation to a new environment. Horses obviously cannot compete on these medications.

Dantrium sodium acts to decrease release of calcium from the calcium-release channel in skeletal muscle and is used to treat malignant hyperthermia. Recent experimental and field studies have shown that when given appropriately, it can significantly decrease signs of rhabdomyolysis in RER horses.^{36,41} Dantrium does not achieve any measurable blood levels when given to horses on full feed; however, when 4 mg/kg PO was given to horses fasted for 12 h, dantrium was detected in plasma 1 h before exercise, and abnormal elevations in CK did not occur after exercise.⁴¹ A dose of 800 mg of dantrium was given to Thoroughbred horses in the United Kingdom 1 h before exercise, and this resulted in significantly lower post-exercise CK activity than a placebo.⁴²

Phenytoin (1.4–2.7 mg/kg, q 12 h, PO) is an alternative medication that has been reported to be effective in preventing rhabdomyolysis in horses with RER.³¹ Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Phenytoin also affects triglyceride metabolism.⁴⁰ Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 µg/ml and not to exceed 12 µg/ml.⁴⁰ Drowsiness and ataxia are evidence that the dose of phenytoin is too high, and subsequently, the dose should be decreased by one-half. Initial dosages start at 6–8 mg/kg orally twice a day for 3–5 days. If the horse is still experiencing rhabdomyolysis but is not drowsy, the dose can be increased by 1 mg/kg increments every 3–4 days. Phenytoin is a monoaminoxidase activator and can affect dosages of other medications. Unfortunately, long-term treatment with dantrolene or phenytoin is expensive, and these drugs must be withdrawn before competition.

Intramuscular injections of vitamin E and selenium are commonly used by veterinarians in an attempt to prevent RER. Horses usually do not have a proven deficiency; however, these supplements are given in an attempt to counteract oxidant injury.⁴⁰ Ensuring adequate oral intake may prevent the muscle soreness associated with IM injections. Daily dietary recommendations for vitamin E and selenium are provided in Table 1.

Various hormones, ranging from thyroxine to progesterone and testosterone, have been given to horses with RER. Initial studies linking low T3 and T4 concentrations in horses with exertional rhabdomyolysis have not been substantiated.^{6,22,43,44} Some mares seem to exhibit signs of rhabdomyolysis 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.

Table 1. Nutritional Requirements for an Average-Sized Horse (500 kg/1100 lb) for RER at Varying Levels of Exertion*

	Maintenance	Light Exercise	Moderate Exercise	Intense Exercise
DE (Mcal/day)	16.4	20.5	24.6	32.8
Percent DE as NSC	<20%	<20%	<20%	<20%
Percent DE as fat	15%	15%	15–20%	20–25%
Forage percent body weight	1.5–2%	1.5–2%	1.5–2%	1.5–2%
Protein (g/day)	697	767	836	906
Calcium (g/day)	30	33	36	39
Phosphorus (g/day)	20	22	24	26
Sodium (g/day)	22.5	33.5	33.8	41.3
Chloride (g/day)	33.8	50.3	50.6	62
Potassium (g/day)	52.5	78.3	78.8	96.4
Selenium (mg/day)	1.88	2.2	2.81	3.13
Vitamin E (IU/day)	375	700	900	1000

Note. NSC refers to the soluble sugar + starch. Fructans in forage are not considered in this calculation as they are not considered likely to impact the glycemic index.

*Daily requirements derived from multiple research studies (%NSC and %fat) and Kentucky Equine Research recommendations. DE, digestible energy; MCal, megacalories; NSC, nonstructural carbohydrate.

Adjunct Therapies

Massage, myofascial release, mesotherapy, stretching, and hot/cold therapy performed by experienced therapists may be of benefit in individual cases of ER.

Diet

A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals are the core elements of treating RER. As with any horse, forage is recommended at a rate of 1.5–2% of body weight as good-quality grass hay. Out of the total daily calories required, it is recommended that <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^a rather than an isocaloric amount of high-starch grain.^{33,35,44} Serum CK activity declined within 1 wk of making the recommended diet change in the five Thoroughbred horses studied by McKenzie.^{27,33,41} The beneficial effects of this type of diet may be caused by the exclusion of dietary starch rather than specific protective effects of high dietary fat. 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 more calm before exercise.^{2,3}

The challenge in altering the diet of Thoroughbred horses with RER is in supplying an adequate number of calories in a highly palatable feed to meet their daily energy demands. This can be very difficult to achieve by blending individual components, but it may be achieved by feeding pelleted, specialized commercial diets. These feeds typically should contain <20% starch or NSC by weight and >10% fat by weight with a high-fiber component. Other feed companies offer similar nutritional content by

blending two or more of their manufactured feeds or by supplementing with additional oils or 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 to design an appropriate diet using recommendation provided in Table 1. The Neuromuscular Diagnostic Laboratory at the University of Minnesota also provides a list of suggested diets together with the results of muscle-biopsy evaluation.

Electrolyte Supplementation

Horses require daily dietary supplementation with sodium and chloride either in the form of loose salt (30–50 g/day) or a salt block. Additional electrolyte supplementation is indicated in hot, humid conditions. Some studies suggest that electrolyte imbalances, as reflected by low urinary FE of sodium or high dietary excretion of phosphorus, may contribute to rhabdomyolysis,²⁴ although others have not found a consistent abnormality.^{13,26,27} Dietary supplementation with sodium or calcium may be of benefit in cases with inadequate sodium or excessive phosphorus excretion.

Other Dietary Supplements

A number of supplements are sold that are purported to decrease lactic acid build up in skeletal muscle of RER horses. These include sodium bicarbonate, B vitamins, branched-chain amino acids, and dimethylglycine. Because lactic acidosis is no longer implicated as a cause for rhabdomyolysis, it is difficult to find a rationale for their use.

A portion of the profits from the sale of Re-Leve^a go to the University of Minnesota.

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