Managing muscle disease in horses

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Since the early descriptions of 'Monday morning disease' (exertional rhabdomyolysis), skeletal muscle disease has long been recognised as a significant problem in the horse. Epidemiological studies have suggested that muscle problems affect up to 6.7 per cent of racing thoroughbreds (McGowan and others 2002) and in some other breeds up to 66 per cent of the population are affected (Valentine and others 2001). Skeletal muscle comprises up to 55 per cent of the body mass of athletic horses (Kearns and others 2002) and has a key role in the metabolism of an individual. It is therefore not surprising that disease processes affecting this organ can have a major impact on the welfare and performance of a horse. This article discusses some common muscle disorders of the horse and ways to manage and treat them.

SKELETAL muscle has a marked ability to regenerate following injury, which is in part due to the presence of satellite cells within the muscle. However, when damage to the muscle is more severe, and disruption of the basal lamina results, irreversible pathology, such as fibrosis, occurs. This leads to permanent disruption of muscle architecture and impedes normal muscle function. The prompt recognition and treatment of muscle damage is therefore critical in minimising these long-term sequelae, and prevention of future episodes will maximise the future performance of horses with underlying muscle diseases.

Horses that are treated for muscle disorders usually present in one of three clinical scenarios:

- With acute focal muscle injuries, such as muscle tears.
- During episodes of acute rhabdomyolysis.
- For the evaluation of poor performance, which may be a result of an underlying myopathy and may or may not be associated with rhabdomyolysis.

Acute muscle injuries

Although acute muscle injuries can be difficult to diagnose, physical examination, ultrasonography and scintigraphy can be used to aid diagnosis. Rest and anti-inflammatory medications are the mainstay of management in these cases. Immobilisation may, in rare cases, be required if there is disruption of the myotendinous unit. Several adjunctive therapies may also have a role in their treatment, at the very least providing symptomatic relief in the acute stages of muscle injury. These include cold therapy, physiotherapy or massage. Although these techniques are applied widely in the treatment of human sports injuries, there is little evidence evaluating their efficacy.

Treatment of acute rhabdomyolysis

Cases of rhabdomyolysis are usually identified based on clinical history, presenting signs and marked elevations in muscle enzyme (creatine kinase [CK] and aspartate aminotransferase [AST]) activity. Myoglobinuria is also supportive of the diagnosis, although this is often not present in milder cases.

Episodes of rhabdomyolysis, possibly associated with over-exertion, may be sporadic in a patient without an underlying myopathy. Several other acquired causes such as exhaustion, hormonal influences, oxidative injury, electrolyte disturbances or infection have been suggested, but evidence for each of these is limited. For example, several studies have reported an over-representation of female animals (MacLeay and others 1999a, McGowan and others 2002), yet a role of sex hormones was not corroborated by studies of muscle enzyme activity throughout the oestrus cycle in thoroughbred racehorses in training (Frauenfelder and others 1986). It is plausible that these acquired factors may modify the clinical phenotype of a horse with a genetic predisposition. In horses where repeated bouts of rhabdomyolysis occur, the presence of an underlying muscle disease should be considered. The two most common inherited diseases associated with episodes of rhabdomyolysis are recurrent exertional rhabdomyolysis (RER) in thoroughbreds (MacLeay and others 1999b) and polysaccharide storage myopathy (PSSM), which has been described in a wide variety of horse breeds (Stanley and others 2009).

There are four main aims when treating horses during acute bouts of rhabdomyolysis. These are summarised in Table 1 and are considered individually below.

Minimising further muscle damage

Affected horses should be confined to a stable with a deep bed, where available, and a number of drugs are often used based on anecdotal efficacy. Non-steroidal anti-inflammatory drugs (NSAIDs), such as flunixin meglumine, are frequently administered to reduce inflammation and provide analgesia, while acepromazine is administered to increase muscle perfusion and will also calm an anxious animal. Anti-oxidants, such as α-tocopherol (vitamin E 5000 iu/500 kg, administered orally every 24 hours), may be beneficial in protecting against free radical damage.

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Table 1: Treatments commonly used for acute rhabdomyolysis

Aim of treatment	Drug	Dose	Comments
Minimise further muscle damage	Flunixin meglumine	0.5 to 1.1 mg/kg intravenously every 12 to 24 hours	Use judiciously in patients with myoglobinuria
	Acepromazine	0.03 to 0.1 mg/kg intravenously or intramuscularly every 8 hours	Administer with care if the horse is severely hypovolaemic
	α-tocopherol	5000 iu/500 kg administered orally every 24 hours	
Correct fluid losses and maintain diuresis	Isotonic oral fluids	6 to 8 litres of water with electrolytes per 500 kg	Use in mild cases of dehydration
	Compound sodium lactate	10 to 20 ml/kg intravenous bolus, followed by 2 to 4 ml/kg/hour for maintenance	Repeat up to four times as required
Provide analgesia	Flunixin meglumine	0.5 to 1.1 mg/kg intravenously every 12 to 24 hours	Use judiciously in patients with myoglobinuria
	Butorphanol	0.02 to 0.1 mg/kg intramuscularly every 4 to 6 hours	
	Lignocaine	Loading dose 1.3 mg/kg intravenously, CRI 0.05 mg/kg/min	
Correct systemic abnormalities	Electrolytes: hypocalcaemia	Calcium borogluconate 40 per cent 0.1 to 0.5 ml/kg intravenously* Calcium gluconate 23 per cent 0.2 to 1 ml/kg*	Correct over two to three hours

CRI, constant rate infusion
* As recommended by Corley and Stephen (2008)

Corticosteroids are not widely used for the treatment of exertional rhabdomyolysis, although they may be of benefit in immune-mediated myositis.

Correct fluid losses and maintain diuresis

Fluid deficits can be severe due to fluid shifts (muscle oedema) and fluid losses (through sweating and previous exercise). The severity of dehydration and the presence of hypovolaemia should be determined by physical examination. In cases of mild dehydration, administration of isotonic oral fluids may be sufficient. However, if clinical signs of hypovolaemia (poor pulse quality, prolonged capillary refill time and jugular fill and cold extremities) are detected, or pigmenturia, as a result of myoglobinuria, is present, then intravenous fluid administration should be initiated as myoglobin is very toxic to the renal tubule cells (Heyman and others 1996) (Fig 1). If intravenous fluids are necessary, polyionic crystalloids are the fluid of choice. Sequential urine samples can then be collected from the horse after administration of intravenous fluids to monitor myoglobinuria (Fig 2).

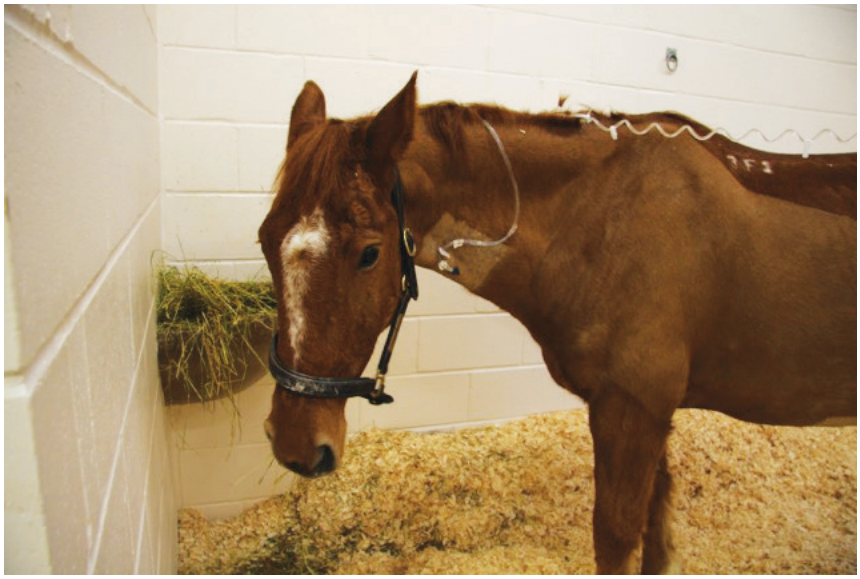

Fig 1: Isotonic intravenous fluids are indicated in the treatment of rhabdomyolysis when myoglobinuria is present or in the face of moderate hypovolaemia. (Image: Matt Smith, Newmarket Equine Hospital)

Urinalysis and the measurement of plasma urea and creatinine concentrations while monitoring urine output in the face of fluid therapy are all useful in assessing renal function. Plasma creatinine should decrease 30 to 50 per cent within the first 12 hours and most horses will urinate once fluid deficits have been corrected. If there is little or no urine production despite correction of hypovolaemia then diuresis should be attempted with furosemide (0.5 to 1 mg/kg, administered intravenously).

Provide analgesia

NSAIDs are often sufficient to control the pain caused by rhabdomyolysis, although they should be administered judiciously in the face of hypovolaemia, particularly in patients with possible renal injury. If additional analgesia is required, opioids may be useful adjuncts and can also be administered as part of a multimodal approach to pain, for example, in conjunction with lignocaine, although this is rarely necessary.

Correct systemic abnormalities

Following muscle injury, horses are frequently hyperkalaemic, hypocalcaemic and hypochloraemic. Plasma electrolytes should be measured before any attempt to correct possible electrolyte disturbances is made. These patients usually have a reasonable appetite and therefore nutritional support is not required. Amino acid supplements have been shown to promote muscle protein synthesis in healthy people (Atherton and others 2010), with varying

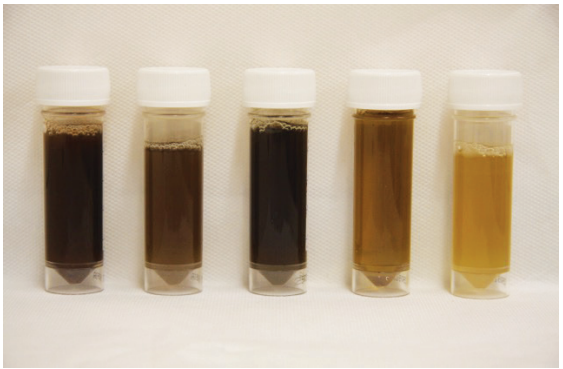

Fig 2: Sequential urine samples from a horse with myoglobinuria secondary to rhabdomyolysis, following the initiation of intravenous fluid therapy

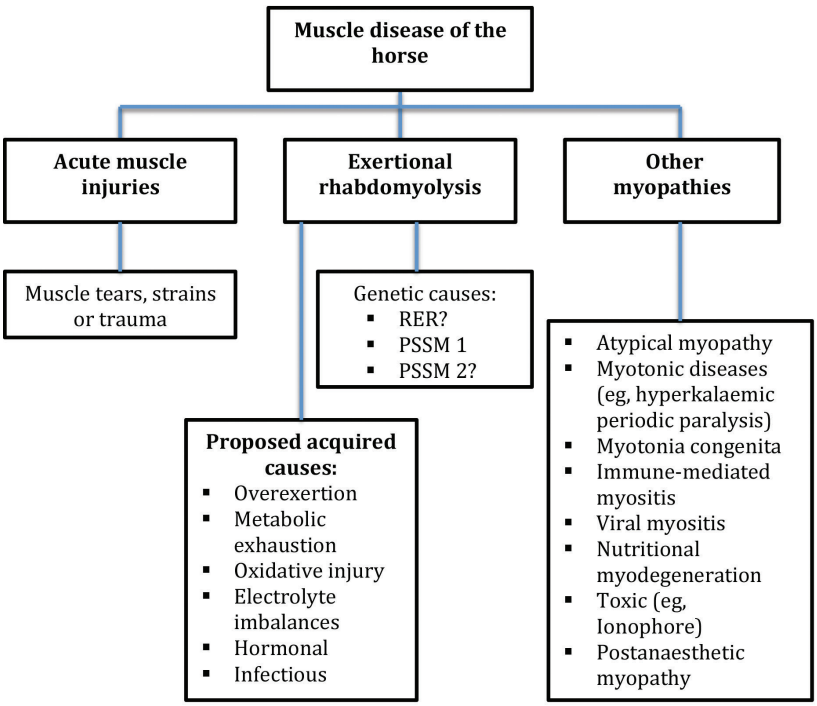

Fig 3: Possible causes of muscle disease in the horse

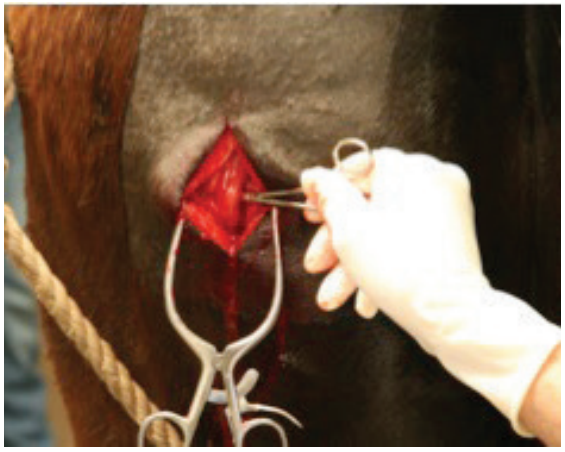

Fig 4: A semimembranosus muscle biopsy sample being collected in a sedated horse following infiltration with mepivicaine

results reported in limiting muscle damage or promoting muscle repair following injury (Sharp and Pearson 2010, Pereira and others 2014). Such supplements may be beneficial during convalescence in the horse, although they should be used cautiously in horses with PSSM because of the potential of leucine to increase skeletal muscle glycogen synthesis (Urschel and others 2010).

Atypical myopathy

In cases where atypical myopathy is suspected (ie, horses kept at pasture without a history of exertion and possibly those with a history of exposure to sycamore trees [Votion and others 2014]), additional treatment with intravenous glucose (1 to 4 mg/kg/minute) may be beneficial to drive energy metabolism away from the defective oxidation of fat. Glucose should be introduced gradually and plasma levels should be monitored. Riboflavin (vitamin B2) is also recommended and is available in many parental multivitamin preparations.

Monitoring

Serum muscle enzyme activity is usually measured 48 to 72 hours following the onset of clinical signs, to confirm that CK activity is reducing and to identify peak AST activity. Levels should then be monitored (usually every seven to 10 days) until a return to baseline is achieved. During this time, gentle in-hand exercise or restricted turnout may be beneficial, particularly in cases of PSSM.

Management of patients with a suspected underlying myopathy

Any disease that affects efferent nerve stimulation, ion channel activity, energy metabolism, calcium homeostasis or sliding of the muscle filaments can disrupt muscle function, often resulting in similar clinical signs. Therefore, further investigation to identify the aetiology of muscle disease in patients with a suspected underlying myopathy may be useful in selecting specific treatments. An underlying myopathy should be considered in patients with recurrent bouts of rhabdomyolysis, elevations of muscle enzyme activity at rest, or moderate increases of muscle enzyme activity (50 to 100 per cent) following exercise. Establishing whether the clinical signs are associated with exercise may be useful in narrowing the list of differential diagnoses, although the genetic causes of exertional rhabdomyolysis may also be associated with vague signs of poor performance only. Fig 3 outlines some possible causes of muscle disease in the horse. Biopsy of the semimembranosus muscle is the mainstay of diagnosis in most cases (Fig 4), although genetic testing is also available on EDTA whole blood or hair roots for the causative glycogen synthase 1 (GYS1) mutation in PSSM1 (McCue and others 2008). Further details on how to perform a semimembranosus muscle biopsy are available at www.rvc.ac.uk/Research/Labs/NeuroLab/MuscleBiopsy.cfm. Biopsy of alternative muscles is occasionally performed, particularly when clinical signs are restricted to other muscle groups.

Low-starch high-fat diets

Dietary management, along with regular exercise, is the mainstay of long-term management of patients with exertional rhabdomyolysis, particularly when a diagnosis of PSSM is confirmed, although these management changes are also often beneficial in horses with RER. In all cases, horses should continue to receive a minimum of 1 to 2 per cent of their bodyweight as forage and, in some cases, additional concentrate feed may not be required. If supplementary feed is necessary to meet caloric requirements, a low-starch high-fat diet providing less than 10 per cent digestible energy as non-structural carbohydrates (NSC) and 15 to 20 per cent fat has been shown to alleviate muscle enzyme responses in horses with PSSM (Ribeiro and others 2004), although less fat than this may be more palatable and sufficient to control the condition. Commercially prepared complete diets are available (such as Dodson and Horrell ERS Pellets or Saracen Re-Leve) or vegetable or maize oil may be added to feed up to a maximum of 1 ml/kg bodyweight per day. When feeding high-fat diets, a feed balancer should be included and, if necessary, vitamin E supplemented to ensure adequate supply of micronutrients. As NSC content is frequently not reported on commercial feeds, liaising with feed companies can be rewarding in formulating an appropriate feeding plan. Dietary changes should always be made gradually over several weeks and full adaptation is likely to take several months. The beneficial effect of these diets may relate to a shift away from glycolytic metabolism or an alteration in the patient's behaviour (reduction in excitability).

Management changes

Dietary changes alone are often not sufficient to control the disease and changes in management are also required. Animals are best managed at pasture with regular exercise (avoiding rest days). Care should be taken at times of the year when the NSC content of the grass is very high, and management such as restricting grazing or using starvation paddocks is recommended. Stress is thought to be a risk factor for episodes of rhabdomyolysis, particularly in horses with RER, and so efforts should be made to minimise changes in routine.

Specific treatments

Dantrolene sodium

Dantrolene sodium is a muscle relaxant that inhibits the release of calcium within the muscle. It has been shown to reduce muscle enzyme activity in response to exercise in thoroughbreds with RER (McKenzie and others 2004) and is used prophylactically in racehorses with anecdotal efficacy. Dantrolene is occasionally used to facilitate a more rapid return to work in horses in training following an episode of exertional rhabdomyolysis. The drug has a fairly short half life; therefore, it is usually given at a dose of 2 to 4 mg/kg one to two hours before exercise.

Vitamin E

Vitamin E, in particular α-tocopherol, may be useful as a free radical scavenger, but deficiencies have also been associated with two specific diseases that affect skeletal muscle: equine motor neuron disease (EMND) and white muscle disease (nutritional myodegeneration). Cases of EMND often present with weakness, muscle fasciculations, muscle atrophy and an elevated tail-head may also be observed. A definitive diagnosis is made on a muscle biopsy harvested from the sacrocaudalis dorsalis medialis muscle. Low plasma vitamin E levels and the presence of a brown pigment (lipofuscin) on the ocular fundus are also supportive of the diagnosis. If EMND is suspected, prolonged treatment with α-tocopherol (vitamin E 5000 iu /500 kg administered orally) is recommended.

Selenium

Combined selenium and vitamin E treatment are recommended for cases of nutritional myodegeneration, typically seen in young foals.

Corticosteroids

Immune-mediated myositis is a rare condition that often follows respiratory infection. Atrophy of affected muscle groups is frequently observed, and biopsy of these affected muscles identifies inflammatory cell infiltrate. In these cases, systemic corticosteroids (dexamethasone 0.05 to 0.1 mg/kg administered intravenously every 24 hours) may be beneficial to suppress the aberrant immune response.

Summary

Prompt treatment of rhabdomyolysis and appropriate long-term management are important in preventing irreversible changes within the muscle architecture that may limit the function of muscle and the future performance of an animal. Acute episodes require rest and anti-inflammatory medication, with particular attention to fluid balance and renal function. Manipulation of exercise and diet are the mainstay of long-term management, while administration of dantrolene may be beneficial, particularly in cases of RER.

What's new?

In 2008, a dominant mutation in the GYS1 gene was identified as a cause of PSSM (McCue and others 2008), leading to the classification of PSSM1 for horses with the GYS1 mutation and PSSM2 for horses that lack the mutation but exhibit similar histopathology. As a result, there is now a genetic test available to diagnose PSSM1, and research continues into the cause(s) of PSSM2, which currently can only be diagnosed on histopathology of muscle biopsy samples. We have recently demonstrated that GYS1 genotype correlates with the severity of histopathology and phenotype in PSSM1 (Naylor and others 2012), suggesting that genotyping cases of PSSM1 may provide useful prognostic information and guide management (eg, in making breeding decisions). Genotyping is performed on EDTA blood or hair roots and is available through the Comparative Neuromuscular Diseases Laboratory at the Royal Veterinary College.

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Notes