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Role of Electrolyte Imbalances in the Pathophysiology of the Equine Rhabdomyolysis Syndrome

P. A. HARRIS[1] and D. H. SNOW[2]

[1]*Department of Comparative Physiology, Animal Health Trust, PO Box 5, Newmarket, Suffolk, CB8 7DW, UK and* [2]*45, Campbell Drive, Wakroonga, New South Wales 2076, Australia*

ABSTRACT. Over a three year period the urinary fractional electrolyte excretion (FE) test was carried out in 144 animals believed to have suffered repeated attacks of the equine rhabdomyolysis syndrome according to their clinical history, clinical presentation and plasma muscle enzyme activities. One hundred animals had FE results outside the expected normal range for the diet they were being fed. Follow-up clinical information was available in 97 of these 100 cases. Seventy-two animals suffered no further attacks of the condition after either the appropriate electrolyte supplementation based on the FE results or the feeding of a diet believed to provide an adequate electrolyte intake in the correct ratios. In 8 of the 72 cases supplementation was stopped, resulting in recurrence of the syndrome. However, restoration of the advised supplementation resulted in no further attacks.

Key words Horses; equine rhabdomyolysis syndrome; electrolyte imbalances.

INTRODUCTION

Over the years there have been many more theories than facts regarding the pathophysiology of the equine rhabdomyolysis syndrome. An underlying abnormality is believed to predispose to the syndrome although the clinical signs appear to be triggered by factors such as exercise. Suggestions for the possible underlying condition include faulty substrate metabolism, vitamin deficiencies, endocrine abnormalities and electrolyte imbalances.[13,14] Several workers have implicated electrolyte disturbances in the pathophysiology of this syndrome[3,5,6,14] and sodium, potassium and/or calcium supplementation has been recommended for the prevention of the condition.[1,3,14] Electrolyte imbalances are difficult to measure simply and routinely.[12] The urinary fractional electrolyte excretion (FE) test has been used to assess electrolyte status in the horse.[6,10,13,19,20]

Recent work has shown that FE values,[13] determined from single spot blood and urine samples collected from clinically normal animals fed a balanced diet, tend to fall within an established normal range (i.e. based on the interpercentile range derived from many clinically normal animals fed such a diet). The feeding of certain diets that are inadequate or imbalanced with respect to their electrolyte content results in single and 24 hour FE values falling outside this reference range. Feeding the appropriate electrolyte supplementation to restore the dietary intake also restores the FE values to within the reference range.[13]

The value of carrying out the FE test on single samples from recurrent rhabdomyolysis sufferers and then feeding an appropriate electrolyte supplement based on the results was investigated.

MATERIALS AND METHODS

Case material

Over a 3 year period FE values were obtained for 144 animals believed to be suffer-

ers of the equine rhabdomyolysis syndrome. This diagnosis was based on clinical history, clinical presentation and plasma muscle enzyme activities. The majority of these animals were 4 years of age or older.

Cases 1–116 were investigated at home by their veterinary surgeon who submitted resting, paired urine and heparinised blood samples to the Animal Health Trust (AHT) laboratories. The following conditions were applied to the collection of samples: 1) the urine should have been a freely voided sample. In mares only, catheterisation was acceptable if a brief trot had been given first; 2) samples should have been collected at least 5 days after a rhabdomyolysis episode; 3) plasma had to be separated as soon as possible after collection, and preferably prior to submission to the laboratory; 4) whenever possible the animal was to have been fed the recommended commercial pelleted feed (i.e. Dalgety Spillers Horse and Pony cubes) if at rest or in light work, plus meadow hay for at least 2 weeks before the samples were collected.

Cases 117–143 were treated as in-patients. Resting, paired blood and urine samples were collected after 2 days on their home feed and water. Following this the horses were placed on a diet believed to provide an adequate and balanced electrolyte intake (i.e. Dalgety Spillers Horse and Pony Cubes plus meadow hay, if at rest or in light work). Dalgety Spillers Racehorse/Eventer Cubes were fed if in hard work. The mean ± SD daily intake from this diet was for a horse in light work 171 ± 1, 85 ± 5, 58 ± 5 and 254 ± 46 mg kg^{-} body weight for calcium, phosphorus, sodium and potassium respectively. Further urine and blood samples were collected after the animals had been on this diet for at least 10 days.

Blood was collected by venepuncture into heparinised collection tubes and the plasma was harvested within 1 hour. Urine was collected by means of a harness system.[12] Plasma and urine were stored at 4°C until analysed for electrolyte and creatinine within 2 days of collection. Glutathione peroxidase activities were measured in all cases as an estimate of selenium status.[18]

Case 144 was investigated at home by its owner, who was a veterinary surgeon, in a similar manner to that described above.

Supplementation

From FE test results the appropriate daily dietary electrolyte supplementation for each animal was determined. The amounts recommended initially depended on the animal's size (e.g. 56 g NaCl for a 500 kg horse and 28 g NaCl for a 300 kg pony). However, in some cases this level of supplementation was inadequate to restore FE values to within the desired range and increased amounts were given.

The animals were then monitored over the following months/years for recurrence of the syndrome. Follow-up resting, paired blood and urine samples were requested after each animal had been on the suggested supplementation for 4 weeks.

Clinical response

To assess whether dietary electrolyte alterations contributed to any clinical response, the degree of improvement was divided into 3 categories using the following criteria:

Improved described the animals that had suffered several episodes prior to referral, had been unresponsive to other managemental changes, and had suffered no further attacks following the relevant recommended dietary changes, for at least 6 months.

?Improved described those animals which had shown an improvement but had possibly only suffered 1 attack prior to referral and/or other changes may have contributed to the recovery.

Not improved identified those animals in which attacks had continued.

Analysis

Creatinine (Cr) was analysed using a method based on the Jaffe reaction adapted for use on a centrifugal analyser (Multistat III, IL).

Table 1. *Division of animals with urinary fractional electrolyte excretion (FE) results within the normal range according to their recent diet, plus the clinical response noted following any dietary advice*

No follow-up samples received

Type of FE result	FE results within normal range		
Diet	Diet changed to that recommended since last attack	Diet changed to that recommended & electrolytes since last attack	Mixed diet ?same electrolyte content as when had attack
Advice	Continue diet as above	Continue diet as above	Feed recommended diet
Number in each group	12	4	22
No follow-up information available	0	0	4
Clinical response			
Not improved	1	–	8
?Improved	3	–	3
Improved	8	4	7
Improved but selenium supplementation also given	1	–	–
Attacks restarted when diet changed	1	1	–

Chloride (Cl) was determined by automatic titration (Corning EE1 920), sodium (Na) and potassium (K) by flame photometry (Corning 480) and phosphate (PO_4) using ammonium molybdate and adapted for use on the centrifugal analyser. Using these results FE values were determined:

$$FE(X) = \frac{(X)\,ur}{(X)\,pl} \times \frac{(Cr)\,pl}{(Cr)\,ur} \times 100$$

where

ur = urinary concentration
pl = plasma concentration
Cr = creatinine
X = electrolyte.

Glutathione peroxidase (Gshpx) was determined using the LKB reaction rate analyser.[18]

RESULTS

Cases treated at home

FE findings in Cases 1–116 were classified into several groups (Tables 1 and 2) together with the degree of clinical improvement found following the appropriate dietary changes. In all cases the above criteria were used to categorise the degree of improvement seen. The ranges of FE electrolyte values considered to be "normal" (Table 3) are based on previous work.[13] The degree of clinical response reported was determined independently of any changes in the FE values.

FE values within the expected normal range (Table 1). The diet of *Cases 1–12* had been changed after their last attack to the commercial cube and meadow hay diet. In each case the owner was advised to continue feeding this diet until the horses were in full

Table 2. *Division of animals with FE results outside the normal range according to the type of FE finding, plus the clinical and FE improvement noted with the appropriate dietary changes*

Type of FE result	FE results outside normal range—mixed diets				
FE finding	Low Na	High PO_4	Low Na High PO_4	High Na	Low Na & K
Number in each group	39	17	10	8	4
No follow-up information available	1	2	0	0	0
Clinical response					
Not improved	2	1	3	1	1
?Improved	2	3	1	2	1
Improved	33	10	6	5	2
Improved but selenium supplementation also given	1	1	–	–	–
Attacks restarted when supplementation stopped	5	2	1	–	–
Follow-up					
Number follow-up samples	20	3	4	2	0
Clinically improved & FE improved[b]	19	3	4	2	–
Clinically improved FE not improved	–	–	–	–	–
Clinically not improved FE improved	–	–	–	–	–
Clinically not improved FE not improved	1	–	–	–	–

[a] The degree of clinical response was determined independently of any changes in FE values
[b] Improved means FE values restored to within acceptable limits.

work, when the cube could be changed to one with a higher energy, protein and electrolyte content (e.g. Spiller's Eventer Cubes). Eight out of the 12 cases improved following these changes. *Cases 13–16* had been placed on the commercial cube and hay diet plus an electrolyte mix supplied by their veterinary surgeon prior to sample submission. Feeding of this supplemented diet was continued and all 4 animals improved. *Cases 17–38* had FE values within the normal range whilst being fed a home mixed diet (i.e. predominantly oat, bran, barley, cube mixes). In many cases the batch of oats and hay had been changed since the attacks, possibly altering the electrolyte content of the diet. Therefore, it was suggested that all these animals should be changed to the commercial cube and hay diet. Unfortunately, it has not been possible to determine if this was carried out in all cases. The importance of electrolyte imbalances in this group of animals could not, therefore, be assessed. All 7 cases that improved and 2 of the 8 cases that did not are

Table 3. *Normal FE ranges*

FE	Commercial cube and hay diet	Predominantly grain based diet (19)
PO_4	0–0.2	0–0.5
Na	0.04–0.52	0.02–1
K	35–80[b]	15–65
Cl	0.7–2.1	0.04–1.6

[a] This range is derived from work carried out in clinically normal horses (in work and at rest) as well as ponies fed a diet believed to provide an adequate and balanced electrolyte intake (based on the commercial Dalgety Spillers cube and hay[13]).

[b] Values up to 100 were considered to be normal if the diet was predominantly roughage.

known to have changed to the recommended diet, but no follow-up samples were received to determine the effect of this diet on their FE results.

FE values outside the normal range (Table 2). Cases 39–116 had FE values outside the "normal" range for their type of diet whether predominantly cube or grain based (Table 3). In those cases with a low FE sodium value, daily sodium chloride (NaCl) supplementation was advised (approximately 56 g NaCl for a 400–500 kg animal). Where both low FE sodium and potassium values were detected, initial supplementation for 2 weeks, with 56 g NaCl and 28 g potassium chloride (KCl) daily, was advised followed by 56 g NaCl only. Calcium supplementation was recommended in those cases where a high FE phosphate value was found (approximately 56 g ground limestone for a 400–500 kg animal). In addition it was suggested that the intake of bran, if fed, was reduced. High FE sodium values tended to be recorded in animals fed excessive salt or given hay grown close to the coast. Decreasing the Na intake or changing the source of hay was advised in these cases.

Fifty-six of the 78 animals with FE values outside the normal range improved clinically following dietary alterations or electrolyte supplementation. Despite a request for repeat samples to ensure that the level of supplementation was adequate, follow-up samples were only received from 29 cases. Of these, 28 came from animals which had improved clinically and in all of these cases FE electrolyte results had returned to within the normal range. In the animal which had not improved FE sodium was still low and remained low despite various dietary manipulations. The horse was eventually destroyed. In 2 cases a low Gshpx value was also found[18] and selenium supplementation was given in addition to the relevant electrolyte.

In 7 of the cases which improved following supplementation, the owners decided to cease feeding the supplement after a while. The attacks then recurred, stopping only when supplementation was restored. An eighth animal was originally diagnosed (i.e. from submitted blood and urine samples) as having a raised FE phosphate value and calium supplementation was advised. This advice was not passed on to a new owner and the animal suffered a further severe attack. Calcium supplementation was resumed and the horse competed successfully as a three-day eventer for the remainder of the season.

Cases treated as in-patients

FE findings on Cases 117–144 while on a balanced diet:

Normal FE values 8 cases Four cases all improved when fed a balanced diet. Of these, one horse also had a low glutathione peroxidase (Gshpx) value[18] and selenium supplementation was given. One case was possibly due to mismanagement as changing the exercise and management regimen in addition to feeding the balanced diet resulted in no further episodes. One case had a degenerative arthropathy of certain thoracic vertebrae. No follow-up was available. One case showed no improvement following various dietary/managemental changes and therapeutic regimens. One case only improved after a month long course of Dantrolene (Dantrium, Norwich Eaton Ltd).

Table 4. *Examples of FE values recorded*

FE: Original results					FE: Following appropriate electrolyte supplementation only			
Low FE Na								
PO_4	Na	K	Cl		PO_4	Na	K	Cl
0	0.003	58	0.5	→	0	0.003	60	2.0
Then further increased Na intake				→	0	0.14	100	2.1
0	0.005	23	1.5	→	0	0.53	40	1.9
0	0.00	30	2.0	→	0	0.15	82	1.5
0	0.008	63	3.1	→	0	0.48	58	2.1
0	0.01	82	–	→	0	0.16	88	0.8
0[a]	0.004	63	1.1	→	0	0.004	66	1.5
High FE PO_4								
0.9	0.21	35	1.1	→	0	0.79	55	0.9
17.0	0.11	34	0.5	→	Not known			
5.8	0.2	69	2.4	→	Not known			
Low FE Na and FE K								
0	0.008	20	1.1	→	Not known			
0.05	0.002	18	0.2	→	Not known			
High FE Na								
0	3.3	44	1.8	→	0	0.61	80	0.9
0	4.1	92	6.8	→	Not known			

[a] This case did not improve clinically despite various dietary manipulations, FE Na also did not improve.

Low sodium FE values: 15 cases. Twelve cases improved. Two had no further attacks but according to their owners were still stiff and lethargic, and one case had a slightly low FE sodium value and showed little improvement either clinically or in FE sodium values with NaCl supplementation.

Low sodium and potassium FE values: 2 cases. Both animals were given NaCl and KCl initially, followed by NaCl alone. One was also given selenium supplementation as the GshPx was low. Both improved.

Low potassium and high phosphate FE values: 1 case. This animal improved with supplementation.

Low sodium and high phosphate FE values: 1 case. Supplementation was advised but no clinical improvement or change in FE values was seen in follow-up samples.

High phosphate FE values: 1 case. This improved with the appropriate supplementation.

No further equine rhabdomyolysis syndrome attacks or elevated AST and CK plasma activities were seen once FE values were within the normal range in 20 of the 28 animals. Dietary electrolyte manipulations resulted in no improvement in 4 animals and a slight improvement in 2 animals. Changing the management regimen helped 1 case and no follow-up information was available for the case which had a radiographic abnormality of its spine.

DISCUSSION

These results suggest that for many animals the feeding of an appropriate electrolyte sup-

plement, based on the results of FE test, may be beneficial in preventing further attacks of the equine rhabdomyolysis syndrome. In a few animals where electrolyte supplementation did not appear to help, imbalances may not have been involved in the pathogenesis. Alternatively, the owners may not have carried out the instructions or the level of supplementation recommended was inadequate. In only one case where clinical improvement had not occurred were follow-up blood and urine samples received. In this case FE values had not returned to the normal range. The amount of supplementation required by the inpatients to restore FE values to within the normal range was found to vary considerably. Therefore, follow-up monitoring should occur.

The findings of this study are complicated because many horse diets are not balanced with respect to their electrolyte content and, therefore, many animals may have abnormal FE values without showing signs of the equine rhabdomyolysis syndrome. The high number of cases that appeared to improve following electrolyte supplementation suggests that the FE test is of value even if abnormal results can occur in animals without a history of the syndrome. It is possible that some horses are better able to adjust to deficient or imbalanced diets than others.

The complication of a deficient or imbalanced diet can be eliminated by feeding an adequately balanced diet. If an abnormal FE value is not then detected, the animal can be kept on this diet with the knowledge that the electrolyte intake should remain constant and any further attacks are unlikely to be related to an electrolyte imbalance. However, because of altered electrolyte requirements in the exercising horse, the test should be repeated when the animal is in full work. If an abnormal FE value is detected when the horse is on an apparently adequate diet, then problems in absorption/utilisation should be considered. Appropriate supplementation can then be given and further FE tests carried out until values fall within the normal range. Difficulties in having owners obtain a complete analysis of their horse's feed resulted in the recommendation that a specific, electrolytically-balanced, commercial pelleted feed should be fed together with hay for 2 weeks prior to FE testing. In the majority of instances, such a diet should have provided an adequate and balanced intake. Unfortunately, a number of owners were reluctant to change the diet to the advised cube and hay.

A lowered Gshpx activity was found in a few animals together with abnormal FE values. Appropriate oral electrolyte and selenium supplementation resulted in the prevention of further clinical attacks of the equine rhabdomyolysis syndrome. However, it is not possible to determine if this apparent recovery would have occurred if either of the measures had been undertaken alone.

Very few studies have been carried out in any species to investigate the effects of slight electrolyte imbalances on muscle function. In man, PO_4 depletion has been found to cause acute rhabdomyolysis under certain circumstances. The cause of the rhabdomyolysis is believed to be a decrease in the adenine pool, an increase in phosphorylation and a slowing of the mitochondrial respiration rate.[4] Workers have shown that in dogs exercise-induced hyperaemia in isolated gracilis muscle was virtually abolished in severely K depleted animals and exercise resulted in rhabdomyolysis.[17] Fatigue, weakness and muscle cramps are common in Na depletion states in man and recovery is usually dramatic when Na is given.[21] Severe hypernatraemia in cats has been shown to result in muscular disturbances, as has hypokalaemia.[8,9]

These reports have shown that marked electrolyte abnormalities can lead to muscular problems. From the present study it would appear that, in the horse, slight deficiencies or imbalances may have a role in the equine rhabdomyolysis syndrome. It is possible that these may cause transient alterations in ionic concentrations across the muscle cell membrane. Deficiencies may alter the number or efficiency of the Na/K pumps

resulting in an alteration in the maximum capacity of the cell to perform active Na and K transport.[7] Potassium, calcium, magnesium, thyroid and energy status and the stage of training may all affect the numbers/efficiency of these pumps.[2,7,11,15,16] These changes may disturb the normal physiological response to exercise which could in turn precipitate equine rhabdomyolysis. In conclusion, although these investigations do not prove that electrolyte abnormalities cause this syndrome, they suggest that the monitoring and correcting of electrolyte abnormalities may be a beneficial preventive measure.

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