Technical Bulletin

Equine Hyperkalemic Periodic Paralysis (HYPP)

Overview and Management Strategies

Definitions:

Hyper — Gk. huper, over, excessive
Kalemic — Lat. kalium, potassium
Periodic — Lat. periodicus, having repeated cycles
Paralysis — Lat. paralusis, inability to move

INTRODUCTION

Equine Hyperkalemic Periodic Paralysis (HYPP) is a co-dominantly inherited disorder of descendants of the Quarter Horse stallion, "Impressive," that affects muscle function. The disorder is characterized by a large variation in symptoms from minor muscle fasciculations to death from heart failure. Diagnosis is available with a genetic test, but management is necessary to lessen or prevent symptoms. People with horses diagnosed with HYPP should work closely with their veterinarians and nutritionists to develop treatment and management programs.

Potassium Metabolism

Potassium is the principal intracellular cation which functions to maintain cell volume and electrical activity. Potassium metabolism is regulated by hormones of the kidneys, adrenal gland, thyroid gland, and pancreas. Potassium readily ionizes in watery environments and is almost 100% absorbed under normal circumstances. It is absorbed almost entirely from the small intestine, with minimal amounts from the large intestine. Potassium is excreted by the kidneys and to a lesser extent in feces, sweat, and skin cells.

Non-exercising horses require 0.3% to 0.4% of dry matter (DM) intake of potassium daily. The requirement can double in hard-working horses. However, common horse feeds supply 0.3% to 6.0% potassium, and horses often ingest 10 times their requirement. Normal horses readily excrete the excess potassium. But, horses with the genetic predisposition to HYPP have been shown to exhibit symptoms when total dietary potassium is greater than 1.1%.

Genetic Mutation

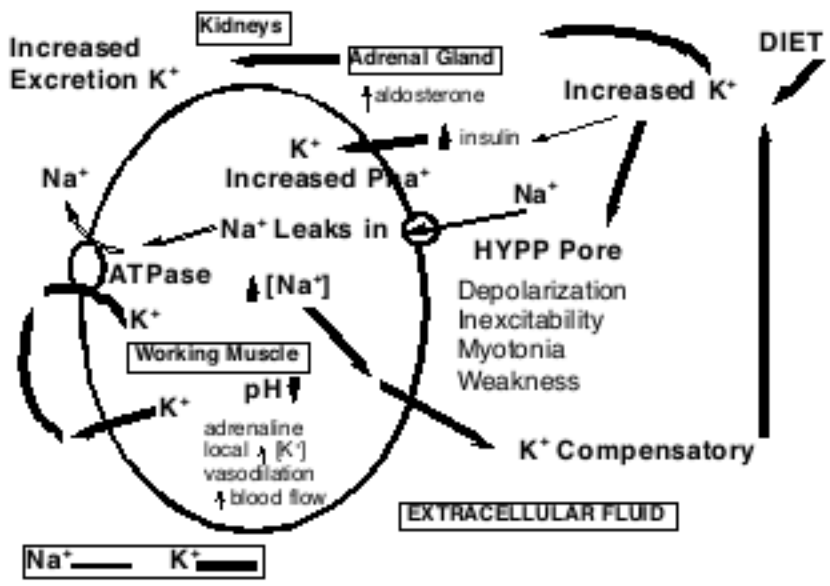
There are currently 18 reported missense mutations in the human adult skeletal muscle sodium channel (SCN4A) that correspond with human disorders such as Hyperkalemic Periodic Paralysis (HPP), Adenemia Episodica Hereditaria, Gamstorp's disease, Hypokalemic Periodic Paralysis, Paramyotonia Congenita, PMC of von Eulenburg, and Myotonia Congenita. Equine HYPP is similar to one human HPP mutation. Acronyms for Equine Hyperkalemic Periodic Paralysis include: HPP, HYPP, HyperPP, and PIPP (Potassium Induced Periodic Paralysis). Equine HYPP is the result of one known point mutation. However, other mutations are possible at any time.

Only one copy of the gene is required for symptoms to occur, and homozygotes (those with two copies) are more severely affected than heterozygotes. Therefore, HYPP is classified as a co-dominant disorder. In one study, HYPP was estimated to affect about 4% of Quarter Horses[1]. However, this estimate is probably quite high for the general population of Quarter Horses (see Frequency of HYPP in Quarter Horses).

Because of a random point mutation, a guanine molecule is substituted for cytosine in the DNA of affected horses causing a substitution of amino acids, leucine for phenylalanine, in the S6 region of domain IV of the alpha-subunit of the voltage-dependent sodium channel protein of muscle cell membranes. The leucine residue is smaller than the phenylalanine residue would be, resulting in a physically or electrochemically generated leaking of sodium through the pore that should remain closed when not under nervous stimulation (that would generate a muscle contraction).

Mechanism of Action

As a result of increased extracellular potassium, sodium leaks into muscle cells through the defective pores. The muscles depolarize and fire, and HYPP symptoms occur. Potassium leaves the cells to compensate for the increased internal sodium concentration, resulting in increased extracellular potassium, and a cycle is created. Potassium excretion by the kidneys and re-uptake of potassium into cells (via Na/K ATPase pump) eventually resolve the situation, or the plasma potassium concentration continues to rise until it slows the normal heart-beat rhythm and the horse dies of heart failure.



Frequency of HYPP in Quarter Horses

From 27,000 blood samples presented to the UC-Davis Veterinary Hospital for testing in 1992-1996 taken from horses tracing to "Impressive":

- 63% were normal (N/N)
- 36% were heterozygous (H/N)
- 1% were homozygous (H/H)

From 1,000 stored samples taken in 1989-1991 from Quarter Horses in general:

- 96% were normal (N/N)
- 4% were heterozygous (H/N)
- 0% were homozygous (H/H)

Clinical Symptoms

There is a wide range of severity of symptoms, ranging from muscle fasciculations, myotonia (muscle stiffness), weakness, yawning, and prolapse of the membrana nicitans (3rd eyelid) to dog-sitting, involuntary recumbency, and spontaneous deaths or euthanasia due to injuries. Horses with HYPP have been found dead in their stalls with no apparent cause. Greatly increased plasma K^+ slows and eventually stops the heart's electrical conduction system, resulting in heart failure. Episodes can be misdiagnosed as rhabdomyolisis (tying-up), colic, seizures, respiratory conditions, or choke.

Diagnosis

Testing of hair roots for the DNA mutation for HYPP is a safe and reliable method of diagnosis. One should ensure the test is performed by a licensed laboratory. Previous methods included electromyograms (EMG) of muscle twitch patterns, electrocardiograms (ECG) of heart rhythms, and the potassium chloride (KCl) challenge. Contrary to popular opinion, high plasma K^+ is not useful for diagnosis of HYPP, because all horses have post-prandial (after meal) variations in plasma K^+ (the severity of which depend on the potassium concentration of the meal) and symptoms can begin at 3.79 mmol/l, which is in the "normal" range for plasma K^+.

RESEARCH FINDINGS

Diet and HYPP

A series of studies was conducted at Texas A&M University to determine the relationship between dietary potassium content, plasma K^+ concentration, and HYPP symptoms.[2,3] Six HYPP H/N and six closely related HYPP N/N broodmares were fed rations of 65% concentrate and 35% coastal hay that provided 1.1, 1.9, and 2.9% potassium in a Latin square designed experiment. The mares were housed in pens, fed individually at 12-hour intervals and not exercised.

There was no difference in potassium absorption or excretion by HYPP status, meaning that expression of symptoms does not occur due to differences in those mechanisms. There was a post-prandial pattern of increased plasma K^+ from the higher potassium diets, but not from the 1.1% potassium diet. An adaptation to lower plasma K^+ occurred by meal 27 when the horses were fed the higher potassium diets. There was increased average plasma K^+ after the 1.9% diet. There was no difference in plasma K^+ by HYPP status at these dietary concentrations (1.1-2.9% potassium).

There were no symptoms (see "HYPP Symptoms Index" sidebar) in N/N horses and no symptoms in H/N horses when they were fed the low potassium diet. The H/N horses had symptoms 52% of the time after the medium potassium diet and 67% of the time after the high potassium diet. Symptoms were twice as common in the daytime as at night. Average plasma K^+ concentration was 3.79 mmol/l at the onset of symptoms. Maximum and average plasma K^+ concentrations were not different by HYPP status. Maximum and average plasma K^+ concentrations were greater after meal 1 than meal 27. The HYPP Symptoms Index was greater after meal 1 than meal 27 and after the high than the medium potassium diet.

In conclusion, non-exercising HYPP H/N horses were maintained asymptomatic with 1.1% dietary potassium fed in two meals. However, HYPP symptoms increased as dietary potassium increased from 1.9% to 2.9%. The onset of HYPP symptoms correlated with plasma K^+ concentration regardless of dietary potassium concentration. A considerable adaptation to the higher potassium diets occurred by day 14, resulting in lessening of symptoms even when diet remained unchanged.

HYPP and Muscling

In 1996, Dr. Naylor presented a hypothesis that HYPP-positive horses have heavier muscling than normal horses.[4] Drs. Spier of the University of California-Davis and Valberg of the University of Minnesota conducted muscle analyses that would support or refute that hypothesis.[1] Using gluteal muscle biopsies, they found no difference in fast/slow twitch percentages or fiber size and no association with clinical severity. Thus, their research did not confirm Naylor's hypothesis.

Age

A common question of horse owners is whether their horse can have HYPP symptoms, even if none have been evident until a certain age. It is important to remember that the main factor that correlates with symptoms, increased plasma K^+ concentration, is not related to age. Therefore, if plasma K^+ concentration reaches the threshold for that horse, symptoms will occur at any age. However, a minor effect, less manifestation of mutant channels with age, has been reported. Also, it has been reported that homozygote foals improve with age. This could be related to the fact that mare's milk K^+ concentration decreases with time:

HYPP Symptoms Index

The HYPP Symptoms Index was created to quantify the severity of symptoms.

- SI = 0 for no symptoms.
- One point for muscle fasciculations on each of five areas of the body — head, neck, shoulders, body, hindquarters.
- One point each for irregular movement of the front and hind quarters.
- One point for third eyelid prolapse.
- Two points for involuntary recumbency.
- Maximum possible score at any time period, SI = 10

Potassium Content of Common Equine Feedstuffs*

	Potassium (%)	g Potassium per lb of feed
High Potassium Feedstuffs		
Sugar beet and cane molasses	4.7	21
Alfalfa hay (90% DM)	1.3–2.3	5.9–10.4
Soybean meal	2.1	9.5
Reed canarygrass	2.5	11.4
Orchardgrass	2.3	10.4
Electrolyte supplements	**	**
Kelp supplements	**	**
Medium Potassium Feedstuffs		
Clover hay (90% DM)	1.5–2.2	6.8–10.0
Fescue hay	1.5–2.4	6.8–10.9
Rice bran	1.4	6.4
Timothy	1.6–1.7	7.3–7.7
Brome	1.7	7.7
Coastal bermudagrass	1.6	7.3
Kentucky bluegrass	1.7	7.7
Oat hay	1.7	7.7
Low Potassium Feedstuffs		
Pure fats and oils	0	0
Beet pulp (unmolassed)	0.9	4.1
Corn	0.4	1.8
Oats	0.5	2.3
Barley	0.5	2.3
Pasture grass (20% DM)	0.7	3.2
Wheat	0.5	2.3
Wheat midds	1.2	5.45
Wheat bran	1.2	5.45
Soybean hulls	1.4	6.4

*Values from NRC, 2007

**Potassium varies depending on product; refer to product label guarantee or have product analyzed for potassium content.

NOTE: Potassium content varies in all feedstuffs. The preceding values are guidelines only, and it is suggested to have all feedstuffs analyzed for potassium content to accurately assess total potassium in the diet.

Potassium Content of ADM Equine Products (as fed)†

	Potassium (%)	g Potassium per lb of feed
GROSTRONG® Minerals (granular)	0.18	0.8
GROSTRONG Mineral Blocks	0.23	1.0
StaySTRONG™ Metabolic Mineral Pellets	0.8	3.6
StaySTRONG 33 Ration Balancer	1.4	6.4
HEALTHY GLO® Nuggets/Meal	1.4	6.4
MOORGLO®	1.4	6.4
SENIORGLO®	1.2	5.4
JUNIORGLO®	1.5	6.8
PRIMEGLO®	1.5	6.8
POWERGLO®	1.4	6.4
Patriot® 36 Ration Balancer	1.4	6.4
Patriot Ultra-Fiber™	1.2	5.4
Patriot Performance (14% protein)	1.0	4.5
Patriot Performance 12-P	1.2	5.4
Patriot Quick Performance™ (14% protein)	0.9	4.1
Patriot Quick Performance 12-10	1.0	4.5
Patriot Mare & Foal	1.3	5.9
Patriot Senior Complete	1.3	5.9
Patriot Feed Easy Complete	1.3	5.9
Forage First® Alfalfa Cubes	1.6	7.3
Forage First Timothy/Alfalfa Cubes	1.5	6.8
Forage First Hay Extender	1.1	5.0

†Values from analysis.

Managing Horses with HYPP

It is most important to minimize the amount of potassium from the diet that reaches the blood at any given time. Also, until more research can be done, do not work horses during peak post-prandial plasma K^+ concentration times (about 2-5 hours after large meals), since they are unlikely to perform well during those times.

In the Texas A&M studies, when the mares were fed two meals per day which contained approximately 33 g of potassium per meal, they remained asymptomatic. However, when fed 58 g/meal and 89 g/meal they had symptoms 52% and 67% of the time, respectively. Therefore, the objective is to feed less than 33 g per meal of potassium and also to feed in multiple meals, or allow horses to eat continuously, so that only small amounts of potassium are available for absorption into the bloodstream at any given time

Management suggestions include:

- Balance the total ration for all other nutrients including fiber
- Keep total dietary potassium below 1.1% and meals below 33 g potassium
- Allow access to paddocks and pastures with low potassium forages
- Give small, frequent meals
- Change diet components slowly
- Supplement with vitamin E, selenium, salt, and balanced minerals with no added potassium (research has shown them to be important in other muscle disorders)

When choosing feeds and feeding programs:

- Do not use electrolyte supplements that contain large amounts of potassium
- Use low and medium potassium feeds
- Minimize the use of "sweet feeds"
- Use vegetable oils as energy sources
- Analyze feeds for potassium content and check labels
- Use continuous rather than meal feeding of fiber sources
- Feed small, frequent meals of concentrates

Management at a Glance

What you should NOT do with horses with HYPP:

- Confine to a stall for 23 hours per day.
- Feed two meals consisting of large amounts of alfalfa, sweet feed, protein supplements, and electrolytes (containing potassium).
- Have no management plan or treatment plan for attacks.

What you should do for horses with HYPP:

- Consult with your veterinarian to develop plans for chronic maintenance and acute treatment during attacks.
- Feed a low potassium diet (< 1.1% in total diet and <33 g potassium per meal). This means you need to know how much potassium is in everything you feed, which is not an easy task.
- Feed as many evenly spaced meals as possible, at least three. (Feeding at 6 a.m., 2 p.m., and 10 p.m. is better than 8 a.m., noon, and 5 p.m.)
- Allow turnout, grazing (low potassium pasture) and exercise as much as possible.
- Do not train or work the horse during peak post-prandial plasma K^+ concentration times (usually about 2-5 hours after a large meal).

- Lactation weeks 1-4 700 ug potassium/g fluid milk
- Lactation weeks 5-8 500 ug potassium/g fluid milk
- Lactation weeks 9-21 400 ug potassium/g fluid milk.[5]

Also, the potassium concentration of mare's milk can be expected to vary according to her dietary potassium concentration.

Gender

Earlier clinical reports suggested that males were more frequently affected than females. However, it is currently believed that both sexes are equally affected.[1] The HYPP mutation is located on an autosomal chromosome, rather than the sex-linked chromosomes.

Symptom Severity

In one study, gluteal muscle samples from 28 horses of varying symptom severity were compared.[6] There was a slight but significant difference in the proportion of mutant to normal mRNA and sodium channel expression with varying symptom severity. Therefore, some horses are expected to have more severe symptoms than others due to slight variations in the amount of mutant sodium channels they possess. However, management is still the largest factor in development of symptoms.

Day vs Night

Symptoms occurred about twice as often during the day as the night in the controlled research study at Texas A&M.[2] A circadian (cycle of day and night) pattern of potassium excretion has been reported in humans,[8] which could explain this finding. NOTE: In a review article,[7] it was mistakenly reported that the Texas A&M study found more symptoms at night rather than during the day.

Homozygous Positive

Horses that are homozygous for HYPP are given the designation H/H. Recent research suggests that HYPP is a co-dominant trait,[9] because these horses, though rare in the population, often have severe laryngeal, pharyngeal, and respiratory difficulties as foals and more pronounced muscle spasms (myotonia) than heterozygotes. It should be remembered that all homozygotes have $HYPP^+$ mothers, while heterozygotes might not. The mare's HYPP status could affect milk potassium concentration.

Adaptation to Diet

In the Texas A&M study, there was no adaptation in plasma K^+ concentration when the horses were fed 1.1% dietary potassium. Higher average plasma K^+ concentrations were seen when the horses were fed 1.9% than 1.1% potassium for 14 days. However, after 14 days of the same diet (1.9% or 2.9% potassium) the horses had much lower peak plasma K^+ concentrations and much lower HYPP Symptoms Index scores. This means that horses fed the same amount of potassium over time do adapt and have less severe symptoms after meals. Remember that sudden changes in diet can result in severe symptoms (when the new diet has a higher potassium content).

Exercise

It is well known that exercise results in increased plasma K^+ concentrations,[10] since K^+ enters the blood from exercising muscle fibers. Increased dietary potassium also results in increased plasma K^+ concentrations. It would be logical to assume that there would be an additive effect on HYPP symptoms when horses consumed large amounts of potassium and were exercised. This is not the case. In fact, walking and trotting tend to lessen HYPP symptoms.

A possible explanation for this finding is that leaking of sodium through the defective pores can only occur when they are closed, in other words, the horse is not exercising. With exercise the pores are open from nervous stimulation. Therefore, walking the horse causes the normal opening of pores, muscular contraction, and closing of pores to replace the abnormal leaking of sodium associated with HYPP symptoms. This also explains why horses with the HYPP mutation, when fed low potassium diets and exercised heavily, do not seem to show symptoms just from the exercise.

Sometimes, horses show symptoms in rest periods after exercise. They are probably the result of dietary potassium being absorbed from the gut (only seen after the horse stops exercising) and are not a result of the exercise, as was previously thought. People tend to associate effects with things that occur directly before them (the exercise) rather than things that occur 2-5 hours earlier (the meals). The peak of plasma K^+ concentration from a meal occurs at about 2-5 hours after the meal. Because of interactions like these, researchers must control diet to study exercise and vice versa. In one report, no effects of exercise were seen in HYPP vs. control horses.[11] But, diet was not controlled, (the horses had ad libitum access to alfalfa hay) so dietary interactions cannot be ruled out.

Other Factors

Other factors such as sleep, resting after exercise, physical stress, weaning, transport, surgery, anesthesia, fasting, and dietary changes have been associated with HYPP symptoms. In many cases these are coincidentally associated with high dietary potassium. There are also hormonal effects on potassium metabolism that are likely to be factors in surgery, anesthesia, and fasting. Research involving dietary control would be required to isolate other causes of HYPP symptoms.

In conclusion, horses with HYPP can be successfully managed with careful attention to diet. Dietary management is the single most important factor affecting HYPP symptoms at this time. Age, gender, and amount of muscle are not important for predicting HYPP symptoms. However homozygotes (H/H) tend to have more severe symptoms than heterozygotes (H/N). More research is needed to clarify the effects of exercise in horses with HYPP.

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