Diagnosis and Medical Management of Endocrine Disorders in Aged Horses

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Aged horses are at risk for pituitary pars intermedia dysfunction (PPID), and insulin dysregulation (hyperinsulinemia and insulin resistance) is an underlying problem in some animals. Hyperinsulinemia and insulin resistance are exacerbated by PPID, and this increases the risk of laminitis. It is therefore recommended that all aged horses be screened for PPID and hyperinsulinemia and the magnitude of these problems be assessed. Endocrine disorders can be successfully managed in aged horses through appropriate husbandry and medical treatment. Author’s address: Department of Clinical Sciences, Tufts Cummings School of Veterinary Medicine, North Grafton, MA 01536 and School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, United Kingdom; e-mail: Nicholas.Frank@tufts.edu. © 2013 AAEP.

1. Introduction

Pituitary pars intermedia dysfunction (PPID) is the most important endocrine disorder of aged horses, with a prevalence rate of 21% recently reported for horses more than 15 years of age.1 Hyperinsulinemia and insulin resistance (IR), which can be collectively referred to as insulin dysregulation, are also concerns in aged horses and can occur concurrently with PPID. Hyperinsulinemia and IR are components of equine metabolic syndrome (EMS) and can remain an underlying problem for the life of the horse or pony. It is likely that EMS has a genetic basis, with the phenotype expressed in the younger animal if obesity is allowed to develop and/or later in life when PPID exacerbates the underlying condition. Equids with PPID can therefore either have lower insulin concentrations and normal insulin sensitivity or hyperinsulinemia and IR, and this can only be determined through diagnostic testing. Testing is highly recommended because hyperinsulinemia and laminitis are associated in equids, with evidence provided by epidemiological studies2,3 and experimental models.4,5 In this presentation, diagnostic testing for PPID, hyperinsulinemia, and IR are reviewed as well as medical treatments for these endocrine disorders.

2. Diagnostic Testing for PPID

When selecting a diagnostic test for PPID, the first question to ask is whether early or advanced disease is suspected. If the horse has advanced PPID, the disorder can be diagnosed on the basis of clinical signs alone. Hirsutism had 71% sensitivity and 95% specificity as a diagnostic test for PPID in horses with postmortem evidence of pituitary disease.6 Although hirsutism is considered pathognomonic for PPID in aged horses, care should be taken to consider the differential diagnoses of chronic systemic disease and malnutrition. Advanced PPID prolongs the anagen phase of hair growth and increases hair length, and the long haircoat of affected horses is better referred to as hypertrichosis rather...
than hirsutism. Although advanced PPID can be diagnosed on the basis of clinical examination alone, it is still advisable to measure adrenocorticotropic hormone (ACTH), glucose, and insulin concentrations before making treatment and diet recommendations.

Early PPID is more challenging to diagnose, and there are two tiers of testing. A plasma ACTH concentration can be measured as a screening test for early PPID. This is the simplest approach to diagnosing PPID, but clinicians are cautioned that some horses with early disease have normal results. To perform this test, a blood sample is drawn and submitted for measurement of ACTH. Plasma ACTH concentrations increase in the late summer and autumn; therefore season-specific reference ranges have been established. It is also important to consider the assay used by the laboratory to measure ACTH and the familiarity of laboratory personnel with equine samples.

Blood is collected by means of jugular venipuncture into plastic tubes containing ethylenediaminetetraacetic acid. Tubes should be placed in a cooler with ice packs or refrigerated and centrifuged the same morning or afternoon of collection.

Interpretation: From November to July, a plasma ACTH concentration >35 pg/mL by chemiluminescent assay confirms the diagnosis of PPID. During the August to October period, an ACTH concentration >100 pg/mL strongly indicates that the horse has PPID, whereas a concentration of 50 to 100 pg/mL is a weak indication of disease. If clinical signs of PPID are present, this equivocal result should be interpreted as positive, and treatment is recommended. However, treatment should not be initiated in horses with ACTH concentrations within this range if there is no historical or clinical evidence of PPID. These horses should be monitored and rechecked in 3 to 6 months.

Because hormone concentrations naturally increase in the late summer and autumn, this time of year should be selected so that the physiological alterations serve as a natural stimulation test. Plasma ACTH concentrations increase in healthy horses during this period, and even higher peaks are detected in those with PPID. It should be noted that this is a new recommendation and reflects a shift in our approach to diagnosing PPID.

The thyrotropin-releasing hormone (TRH) stimulation test is the second tier test for detecting early PPID. This test was developed by Dr Jill Beech at the University of Pennsylvania and is thought to be the most sensitive diagnostic test for PPID available at present. Although it is referred to as a second-tier test, it is also appropriate to perform this test as a first-tier approach. This is likely to become the recommended approach in the future because protirelin (synthetic TRH) is made available to practitioners by pharmacies. Testing is not recommended during the August-to-October period at present because season-specific cutoff values have not been established.

Fasting is not required for this test. A baseline (time = 0) blood sample is collected, and 1.0 mg (total dose) TRH is then administered IV as a bolus. A second blood sample is then collected 30 minutes later. Blood samples are handled as described above, and plasma is submitted for the measurement of ACTH concentrations.

Interpretation
- Baseline ACTH concentrations are interpreted as described above.
- Results are negative if ACTH concentration is <35 pg/mL (chemiluminescent assay) at 30 minutes.

There is a strong indication of PPID if the ACTH concentration is >75 pg/mL at 30 minutes when testing is performed from November through July. There is a weak indication of PPID if the ACTH concentration is between 35 and 75 pg/mL at 30 minutes when testing is performed from November through July.

Some clinicians prefer to collect the second blood sample at 10 minutes and interpret the results (November through July) as follows: Negative if <85 pg/mL, weak indication if 85 to 100 pg/mL, and strong indication if >100 pg/mL. Research to establish reference intervals is ongoing.

3. Diagnostic Testing for Hyperinsulinemia
Testing for hyperinsulinemia is recommended for all aged horses with clinical signs of endocrine disorders or laminitis. The author also recommends screening horses for hyperinsulinemia as part of routine health checks in the same way that humans are screened for hypercholesterolemia. High-risk populations for hyperinsulinemia include pony, Morgan horse, Paso Fino, and Arabian breed groups, as well as any horse with generalized obesity or obvious regional adiposity. Aged horses are placed in the high-risk category if PPID is developing or there is a history of EMS.

Fasting insulin concentrations were previously recommended as the diagnostic test for hyperinsulinemia in horses, but this recommendation has changed recently. When fasting insulin concentrations are measured, a cutoff value of 20 μU/mL is recommended for the general population if the radioimmunoassay is used. Breed-specific reference ranges are also being developed. The glucose concentration should be measured in the same sample to detect hyperglycemia, and diabetes mellitus has
been associated with PPID in aged horses. Fast- ing conditions are achieved by leaving only one flake of hay with the horse after 10 PM and drawing blood the next morning, or feeding as normal in the morning and then collecting the blood sample after 4 PM.

An oral sugar test (OST) has been introduced to better assess postprandial hyperinsulinemia in equids, and this test detects insulin dysregulation in horses with normal fasting insulin concentrations. The test is performed by fasting the horse as described above and then administering corn syrup at a dosage of 0.15 mL/kg PO (75 mL for a 500-kg horse). Syrup is given by mouth with the use of 60-mL catheter-tip syringes, and blood samples are collected for glucose and insulin measurements 60 and 90 minutes later. The owner can administer the corn syrup before the veterinarian arrives.

Interpretation

- Results are normal if the insulin concentration is <45 µU/mL (radioimmunoassay) at 60 and 90 minutes.
- Results indicate hyperinsulinemia if the insulin concentration is >60 µU/mL at 60 or 90 minutes.
- Results are considered equivocal if the insulin concentration is 45 to 60 µU/mL at 60 or 90 minutes. Testing is repeated at a later time, or the combined glucose-insulin test should be considered.
- Results indicate an excessive glucose response if the glucose concentration is >125 mg/dL at 60 or 90 minutes.

Owners sometimes express concern about administering corn syrup to horses with suspected hyperinsulinemia or laminitis. Problems have not been encountered in the author’s experience, but a two-step approach can be adopted if necessary. The first step is to measure the fasting insulin concentration. If the concentration is >20 µU/mL, then this result provides evidence of insulin dysregulation and further diagnostic testing is optional. It is still helpful to perform an OST in a horse with modest hyperinsulinemia to assess insulin responses to oral sugars and to make diet recommendations, but this is not essential. If the fasting insulin concentration is <20 µU/mL, then the OST is recommended to complete the evaluation, and the owner can be reassured that the test is safe to perform in their horse.

Resting triglyceride and leptin concentrations can provide additional information in the management of endocrine disorders in aged horses. Hypertriglyceridermia has been identified as a predictor of laminitis risk in ponies, with cutoff values of 57 and 94 mg/dL established from two studies of the same population. A lower cutoff value of 27 mg/dL has been proposed for horses by McCue et al after reviewing data from an EMS genetics study, and breed-specific reference ranges may be forthcoming. Leptin concentrations can be measured for diagnostic purposes if blood samples are sent to the Cornell Animal Health Diagnostic Laboratory (Ithaca, New York). When horses of approximately the same body condition score were compared, horses with high leptin concentrations (>12 ng/mL) had significantly lower insulin sensitivity than those with normal leptin concentrations (<2 ng/mL). Higher-than-normal leptin concentrations (>4 ng/mL) indicate that adipose tissues are abnormal and secreting excessive amounts of leptin.

Other markers of metabolic dysregulation may be incorporated into diagnostic panels in the future. Wooldridge et al recently validated an ELISA for high-molecular-weight adiponectin and reported concentrations of 3.6 ± 3.9 µg/mL (mean ± SD) and 8.0 ± 4.6 µg/mL for obese and lean horses, respectively. Serum amyloid A and ferritin concentrations are also associated with obesity and insulin resistance and may provide additional evidence of metabolic dysregulation.

4. Medical Management of PPID

Pergolide mesylate is administered to horses with PPID to restore dopaminergic inhibition of melanotrophs. This ergot alkaloid drug binds to D2 receptors and inhibits proopiomelanocortin hormone synthesis. Pergolide is prescribed at a starting dose of 0.002 mg/kg (1 mg for a 500-kg horse), and the dosage range extends to 0.01 mg/kg (5 mg for a 500-kg horse). Approximately 30% of horses exhibit anorexia when treatment is initiated, and this problem can be avoided by starting with half of the dose for the first 2 days.

Cyproheptadine can be administered in combination with pergolide at a dosage of 0.25 mg/kg PO q 12 hours. When these drugs were compared as single treatments, pergolide was more effective. Seventeen of 20 horses (85%) with PPID improved after pergolide treatment, compared with only two of seven horses treated with cyproheptadine. Cyproheptadine antagonizes serotonin, which is thought to be a stimulatory neurotransmitter for pars intermedia melanotrophs, and mild sedation is an occasional side effect of treatment. The author considers cyproheptadine therapy as an additional treatment when the horse reaches a pergolide dosage of 0.006 mg/kg (3 mg/d for a 500-kg horse).

The goals of medically managing PPID in an aged horse depend on disease severity. In early PPID, the pergolide dosage should be adjusted until plasma ACTH concentrations return to reference range, with adjustments after 30 days. However, this goal cannot be attained in some advanced cases. Clinical signs are important to monitor in both situations, and the primary goal when treating advanced PPID is to achieve a clinical response. This response can sometimes be seen when pergolide is administered at a lower dosage over a long period of time, so even owners with financial limitations.
should be encouraged to provide treatment. Ideally, the dosage of pergolide should be increased in advanced PPID cases until ACTH concentrations exhibit a downward shift, which indicates a response, even if concentrations remain above reference range. Treatment of PPID is particularly important when glucocorticoid-mediated IR exacerbates underlying hyperinsulinemia. Insulin concentrations decrease and insulin sensitivity improves with better control of PPID, and this may lower the risk of laminitis.

5. Dietary Management of PPID

Fasting insulin concentrations and OST results are normal in some horses with PPID and abnormal in others. This is consistent with the theory that PPID exacerbates hyperinsulinemia, and most horses improve with pergolide treatment. However, care must still be taken to provide the appropriate diet if hyperinsulinemia persists. A diet composed of hay, low-sugar/low-starch pellets, and vegetable oil (one-half to 1 cup twice daily) should be selected, and pasture access should be limited. In contrast, horses with PPID that do not have problems with postprandial hyperinsulinemia can be provided with senior feeds and free access to pasture.

6. Medical Management of Insulin Dysregulation

Before a management plan is formulated, it must first be determined whether known exacerbating factors for hyperinsulinemia and IR, including obesity, high-sugar feeds, and PPID, are present. Relationships between obesity and insulin sensitivity in equids are not as straightforward as they might seem. Body fat mass is negatively correlated with insulin sensitivity in equids, and yet some obese horses have profound hyperinsulinemia whereas others have normal insulin values. Genetics are likely to play an important role in determining the magnitude of insulin dysregulation associated with obesity. If it is accepted that insulin dysregulation is genetically determined, then obesity is better viewed as an exacerbating factor; this is supported by the finding that hyperinsulinemia and IR are detected in nonobese horses. In the author’s experience, insulin values improve with weight loss in most obese horses with hyperinsulinemia. Whether obesity is a cause or an exacerbating factor for hyperinsulinemia, there are other health risks associated with this problem, and horses should be maintained in appropriate body condition. Equine obesity is a major concern in the United States, with a study of horses in Virginia revealing prevalence rates of 32% for the overconditioned state and 19% for obesity. Although owners are sometimes concerned about older horses losing condition as they age, obesity should not be promoted through overfeeding. Aged horses that are obese should be placed on a weight reduction diet. A concept of weight loss resistance has been proposed to describe the marked individual variability in responses to dietary interventions, and this is a familiar situation for veterinarians managing obesity in equids.

Pituitary pars intermedia dysfunction is also an exacerbating factor for hyperinsulinemia and IR and should be controlled with pergolide treatment. Some affected horses have a history of obesity but have lost body fat mass and only retain regional adiposity within the neck and tailhead regions. Others are still obese when PPID first begins, and we must rely on subtle signs of pituitary dysfunction, including delayed shedding of the winter haircoat.

There are two indications for pharmacological intervention in the management of insulin dysregulation in aged horses. The first is the acceleration of weight loss in obese animals and the second is management of postprandial hyperinsulinemia after exacerbating factors have been managed.

7. Levothyroxine Sodium

Levothyroxine accelerates weight loss in horses that are placed on a controlled diet, and this is accompanied by increases in insulin sensitivity. Pre-treatment with levothyroxine for 14 days also prevented healthy horses from developing IR after endotoxin infusion. Levothyroxine is administered at an approximate dosage of 0.1 mg/kg, which is rounded to 48 mg/d for horses weighing 450 to 525 kg. A mild state of hyperthyroidism is induced and sustained for 3 to 6 months until body fat mass decreases. When levothyroxine is discontinued, the dosage should be lowered to 0.05 mg/kg for 1 week and then 0.025 mg/kg for a second week.

8. Metformin Hydrochloride

Because the oral bioavailability of the available metformin formulation is low (7.1 ± 1.5% in fasted horses), it has been questioned whether the established effects of this drug on insulin sensitivity in humans occur in horses. Additional information was recently provided to resolve this question when Durham et al demonstrated that metformin (30 mg/kg) given orally 30 minutes before an oral glucose tolerance test significantly lowered glucose and insulin concentrations. These findings suggest that metformin can limit postprandial hyperinsulinemia even if its effects on insulin sensitivity are weak. The current recommendation is therefore to administer metformin at a dosage of 30 mg/kg, given 30 to 60 minutes before feeding. Metformin is available as 1-gram tablets and is well tolerated with the exception of oral irritation in some horses.

9. Ethical Considerations

The author consults on study design for Boehringer Ingelheim Vetmedica, Inc.

References and Footnotes

1. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary...

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