INTRODUCTION

We will discuss medical treatment of pituitary pars intermedia dysfunction (PPID) and Equine Metabolic Syndrome (EMS). These endocrine disorders require management as well as medical treatment, so it is important to institute appropriate housing, diet, and exercise changes.

TREATMENT OPTIONS FOR PPID

Pituitary pars intermedia dysfunction, which is also called equine Cushing’s disease, develops when melanotropes within the pars intermedia of the pituitary gland secrete larger amounts of hormones derived from the prohormone proopiomelanocortin (POMC). In the pars intermedia of a healthy horse, the end products of the POMC pathway are alpha melanocyte-stimulating hormone (αMSH), beta-endorphin, and corticotrophin-like intermediate peptide (CLIP). When PPID develops, secretion of αMSH and CLIP increases and other hormones derived from POMC are also released. These hormones include adrenocorticotropin hormone (ACTH), which is the primary product of the POMC conversion pathway in the pars distalis. Secretion of ACTH from the pars intermedia induces hyperadrenocorticism because production of this hormone is unregulated in this region of the pituitary gland. The pars intermedia does not secrete ACTH under normal circumstances, so it is not under negative feedback control through the hypothalamic-pituitary-adrenal axis.

Loss of dopaminergic inhibition creates a permissive environment for hyperplasia or neoplasia within the pars intermedia. Dopamine is an inhibitory neurotransmitter that acts on D2 dopamine receptors and reduces the activity of melanotropes. This neurotransmitter is secreted by dopaminergic neurons that have their cell bodies within the paraventricular nuclei of the hypothalamus and extend down to the pars intermedia. These dopaminergic neurons degenerate over time as a result of oxidative damage. It is assumed that dopaminergic neuron degeneration is enhanced in horses with PPID, which leads to pituitary hyperplasia, hypertrophy, and the formation of functional pituitary adenomas.

Pergolide mesylate – This ergot alkaloid dopamine receptor agonist is administered to horses with PPID to restore dopaminergic inhibition of melanotropes. Interaction with D2 receptors inhibits hormone secretion and is therefore associated with improvement in clinical signs. It has not been determined whether pergolide treatment also inhibits the development of pituitary hyperplasia or reduces the size of pituitary adenomas, but these beneficial effects are plausible considering the mechanism of action of this drug. Pergolide was previously marketed as Permax® (previously manufactured by Eli Lilly Co) and used for the treatment of Parkinson’s disease. However, this product was voluntarily withdrawn from the market in March 2007 after the Federal Drug Administration issued a warning that pergolide was associated with increased incidence of valvular regurgitation in people. Since that time, pergolide has only been available through compounding pharmacies. This has lowered the price of the drug, but also raised concerns about the stability and efficacy of compounded pergolide. At present, the recommended approach is to purchase pergolide in granule form and assume a 60-day shelf life or as an aqueous suspension and assume a 30-day shelf life. In a recent study, Davis et al. demonstrated that pergolide lacked stability over a 35-day period when prepared as an aqueous suspension. This group also showed that higher temperatures and exposure to light enhanced degradation, so aqueous preparations should be stored in dark containers and refrigerated. Even under these conditions, a maximum 30-day shelf life should be assumed for aqueous preparations. Pergolide is prescribed on a total dose basis, using a starting dose of 1.0 mg/day for horses and ponies with PPID. If the horse owner is willing to administer half the dose twice daily, this may be preferable on the basis of recent pharmacokinetic data. Some owners report loss of appetite when pergolide is first started. If anorexia develops, treatment should be halted for 2 days or until appetite improves, and then restarted at 0.25 mg/day for 2 days, 0.5 mg/day for 2 days, and 0.75 mg/kg for 2 days. Another side effect of pergolide treatment is temporary dullness after initiating therapy and this can be addressed using the same strategy. Pergolide is currently purchased from compounding pharmacies as a 1.0 mg per 2 mL suspension and costs approximately $1.60/day for a horse receiving 1 mg/day.

Cyproheptadine – Both pergolide and cyproheptadine lower plasma ACTH concentrations in PPID horses, but pergolide is more effective. Donaldson et al. reported that 17 of 20 horses (85%) with PPID improved with pergolide treatment, compared with only 2/7 horses treated with cyproheptadine. Cyproheptadine antagonizes serotonin, which is thought to be a stimulatory neurotransmitter for pars intermedia melanotropes. Treated horses occasionally exhibit sedation when
treatment is initiated. A dosage of 0.25 mg/kg PO q12h is recommended and the drug is available as 4 mg tablets in labeled (Periactin®, Merck & Company, Inc.) and generic forms. At present, tablets cost approximately $0.50 each ($14/day for a 450-kg horse), so most practitioners order the drug from compounding pharmacies. Cyproheptadine is compounded into an aqueous suspension at 50, 100, or 150 mg/mL concentrations and costs approximately $1.30/day for a horse weighing 450 to 525 kg.

**Trilostane** – This drug is a 3-beta hydroxysteroid dehydrogenase inhibitor, so it acts by inhibiting cortisol synthesis within the adrenal cortex. Trilostane is commonly used in dogs for the management of pituitary-dependent hyperadrenocorticism when increased ACTH secretion from a pars distalis adenoma induces adrenal hyperplasia. However, the reported incidence of adrenal hyperplasia is low (20%) in horses with PPID, so this may limit the usefulness of trilostane in this species. Despite this theoretical assumption, McGowan and Neiger†̅ reported improvement in clinical signs in 20 horses with PPID that were treated with trilostane at a mean dosage of 0.5 mg/kg. Lethargy resolved, polyuria/polydipsia decreased, and recurrent or chronic laminitis improved in 13/16 affected horses. Combined dexamethasone/thyrotropin-releasing hormone test results improved after treatment, but did not return to normal. The recommended dosage of trilostane has subsequently been increased to 1.0 mg/kg (q24h; given in the evening). Trilostane is now approved by the Federal Drug Administration for the treatment of hyperadrenocorticism in dogs and is marketed in the United States as Vetoryl® (Dechra Veterinary Products). This product is only available as 60 mg capsules and is very expensive for horses (approximately $100 for 30 capsules; $26/day for a 500-kg horse; $800/month). Trilostane treatment is therefore reserved for cases where ACTH stimulation test results indicate significant adrenal involvement.

**Combination therapy** – Some horses with PPID respond to combination treatment with pergolide and cyproheptadine. One approach is to reach the maximum pergolide dosage of 5 mg/day and then add cyproheptadine treatment (0.25 mg/kg PO q12h) to the regimen. Other clinicians with experience in this field add cyproheptadine when the pergolide dosage reaches 3 mg/day.†̅

**RESPONSE TO PPID TREATMENT**

**Clinical signs and behavior** – Although pergolide sometimes induces transient mental dullness when treatment is started, most horses respond positively by exhibiting increased physical activity and energy. Polyuria and polydipsia often resolve with treatment and skeletal muscle mass can improve over time, particularly in animals that are still being ridden. Effects of treatment on hair shedding take longer to recognize, but many horses show improvement in shedding the following season. Improvement in laminitis has also been reported. Horse owners should always leave precautionary measures in place to prevent laminitis, but laminitis risk appears to decrease with pergolide treatment. Horses with pre-existing insulin resistance that has been exacerbated by PPID should be monitored by rechecking insulin concentrations. One commercial laboratory (Cornell University Animal Health Diagnostic Laboratory) offers an ACTH and insulin panel ($38/sample) that can be run on a single EDTA plasma sample. In the author’s experience, plasma insulin concentrations decrease when pergolide treatment is initiated in horses with PPID and hyperinsulinemia.

**Plasma ACTH concentrations and dexamethasone suppression test (DST) results** – Whichever test was performed to diagnose PPID should be repeated 4 weeks after treatment is initiated. If PPID was diagnosed on the basis of an elevated plasma ACTH concentration, a goal of treatment should be to return concentrations to within reference range (< 35 pg/mL by chemiluminescent assay). However, ACTH concentrations vary over time in horses, so small alterations should not be over interpreted. If the plasma ACTH concentration is still significantly (> 10 pg/mL) above reference range at the 4-week recheck, the pergolide dosage should be increased (0.5 or 1.0 mg/day). This procedure is repeated until a maximum pergolide dosage of 5 mg/day is reached. If plasma ACTH concentrations remain elevated at the maximum dosage, combination therapy should be considered. Alternatively, the clinician should take a pragmatic approach and decide upon a dosage that is economically feasible, yet still beneficial to the patient. If the DST is used to diagnose PPID, the pergolide dosage should be increased until cortisol concentrations < 10 ng/mL (1.0 μg/dL) are detected 19 or 24 hours after dexamethasone administration. Failure to suppress after 4 weeks indicates that the dosage should be increased. Both plasma ACTH concentrations and the DST are affected by season, so this should be considered when scheduling follow-up testing. Higher ACTH concentrations and false positive DST results are detected in the late summer/autumn period (September and October in Tennessee).†̅

**TREATMENT OPTIONS FOR EMS**

Equine metabolic syndrome is a disorder that should be managed with diet, housing, and exercise changes, rather than drugs in the majority of cases. Veterinarians have a responsibility to recommend management changes and
discourage horse owners from administering drugs as a substitute. However, there are two indications for pharmacological intervention: 1) short-term (3 to 6 months) treatment while management changes are taking effect and 2) refractory cases. Two drugs have been examined to date:

**Levothyroxine sodium** – The Thyro L® product manufactured by Lloyd, Inc. has been evaluated in several studies conducted by the author’s research group. Administration of levothyroxine at higher dosages has been associated with weight loss and increased insulin sensitivity, and pretreatment with levothyroxine for 14 days prevented horses from developing insulin resistance after endotoxin infusion. Levothyroxine has been administered at an approximate dosage of 0.1 mg/kg, which has been rounded to 48 mg/day for horses weighing 450 to 525 kg. It is assumed that levothyroxine induces weight loss by raising circulating thyroxine concentrations and stimulating basal metabolic rate. Serum thyroxine concentrations rise to between 40 and 80 ng/mL (reference range: 10 to 40 ng/mL) in treated horses, but clinical signs of hyperthyroidism are not observed. Weight loss is enhanced by restricting caloric intake and increasing exercise at the same time that levothyroxine is administered. Horses should not be allowed free access to pasture during treatment because levothyroxine is likely to induce hyperphagia, which offsets the effects of treatment. Levothyroxine is primarily administered for the purpose of accelerating weight loss in obese horses and can be prescribed for 3 to 6 months while other management practices are instituted. In a recent study obese horses with chronic EMS were treated with levothyroxine without caloric restriction to determine whether the drug was still effective in animals with normal caloric intake. Interestingly, a higher dosage of 72 mg/day (approximately 0.15 mg/kg) was required to induce significant weight loss and improvement in insulin responses in these severely affected horses. Current recommendations are therefore to initiate treatment at 48 mg/day (with restricted caloric intake) and then increase to 72 mg/day after 3 months if the horse remains obese. Most horses are treated for 6 months and then taken off the drug by administering 24 mg/day for 2 weeks and then 12 mg/day for 2 weeks. A level scoop of Thyro-L® powder contains 12 mg levothyroxine. Some horse owners and veterinarians leave horses on a “maintenance” dose of levothyroxine (12 to 24 mg/day), but there is no scientific evidence to support this approach. At the time of writing, Thyro-L® can be purchased for $25 (1 lb; 1,000 mg; 83 teaspoons) or $175 (10 lb). Each pound of Thyro-L® contains 1,000 mg levothyroxine (approximately 80 teaspoons), so this treatment costs < $1 per day for 48 mg/day and < $1.50 per day for 72 mg/day if a 10-lb container is purchased.

**Metformin hydrochloride** – Glucophage® (Bristol-Myers Squibb) and generic forms of metformin have been used for decades in human medicine. Metformin is a biguanide drug that is administered to control hyperglycemia and increase tissue insulin sensitivity in humans with diabetes mellitus. This drug suppresses hepatic glucose production by activating AMP-activated protein kinase, which inhibits gluconeogenesis and lipogenesis while increasing fatty acid oxidation and lipolysis. Two key gluconeogenesis enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase are inhibited by metformin through this mechanism. The insulin-sensitizing effects of metformin may also be mediated by skeletal muscle AMPK, causing increased glucose transporter 4 abundance within cell membranes and enhanced glucose uptake. One study also describes AMPK-independent effects of metformin on cardiac muscle, with results indicating that p38 mitogen-activated protein kinase (p38 MAPK) and protein kinase C pathways are activated. Only a small number of studies have been performed to date in horses. Durham et al. reported that resting insulin concentrations and proxy measures of insulin sensitivity improved in horses and ponies with presumed insulin resistance when treated with metformin at a dosage of 15 mg/kg PO q12h. Administration of metformin at this dosage was associated with positive clinical outcomes, but Hustace et al. subsequently reported that the oral bioavailability of 3 grams metformin was 7.1 ± 1.5% in fasted horses and 3.9 ± 1.0% in fed animals. Our current recommendation for metformin is therefore 30 mg/kg PO q12h. This drug is available as generic tablets and at the time of writing is available from a veterinary pharmacy at a cost of $140 for 1,000 tablets (1 gram/tablet). A 500-kg horse receives 15 tablets twice daily, so 900 tablets are required per month (approximately $125/month).

**Response to treatment** – Weight loss can be monitored using a weight tape or walk-on scale and neck circumference measurements may be useful for assessing improvement in regional adiposity. Fasting blood glucose and insulin concentrations and combined glucose-insulin test results should return to normal with treatment. However, there are some patients that remain insulin-resistant in the face of management changes and medical treatments. These animals remain at higher risk for laminitis, so every effort should be made to avoid triggers for this disease. Severely affected horses and ponies should be held off pasture and housed in dry lots or small grass paddocks.

**DIABETES MELLITUS**

Affected horses suffer from persistent hyperglycemia and sometimes glucosuria. This condition becomes a greater concern when glucosuria causes electrolyte depletion and anorexia. Diabetic horses are more susceptible to hypertriglyceridemia when stress and negative energy balance stimulate lipid mobilization, and this can occur when other
medical problems develop such as gastrointestinal disease. Horses with diabetes mellitus that are in good general health should be managed with dietary changes and administration of metformin, whereas patients in crisis require exogenous insulin. Short-acting regular (soluble) insulin can be administered intravenously as a constant rate infusion or long-acting insulin can be given via subcutaneous injection. The decision to administer insulin is based upon the degree of glucosuria and hypertriglyceridemia. Diabetes mellitus is sometimes associated with PPID, so pergolide should be administered to these patients.

REFERENCES


