DO ALL HORSES WITH PPID NEED MEDICAL TREATMENT?

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Introduction

Management of equids with PPID includes husbandry and adequate nutrition. The dopaminergic drug pergolide (Prascend™) remains the medication of choice for PPID. The decision to use pergolide should be made on a case-by case basis.
Management of equids with pituitary pars intermedia dysfunction (PPID) consists of improved husbandry, including proper nutrition and limiting competition for feed, body-clipping, preventive health care, dentistry, and appropriate treatment of concurrent medical problems. In addition, specific treatment with the dopamine agonist pergolide can improve quality of life and reverse many clinical signs of PPID. Combination treatment with both pergolide and cyproheptadine, in the author's experience, may also prove beneficial in more advanced cases. Assessment for concurrent glucose and insulin dysregulation, especially in patients with laminitis, is also warranted. Management of these latter conditions requires appropriate feeding and exercise programs, proper hoof care, judicious use of analgesic medications, and in some cases use of additional medications (metformin and levothyroxine) may be considered. Finally, due to costs of lifelong medication(s), the extent of treatment of PPID-affected equids should be made on a case-by-case basis, in consideration of the client's goals.

Learning Objectives

1. Recommend husbandry and nutritional considerations
2. Understand medications for the treatment of PPID
3. Review the Prascend™ field efficacy study and extended use studies
4. Summarize current treatment recommendations and prognosis

Husbandry and nutritional considerations: In the earlier stages of PPID, when hypertrichosis may be the primary complaint, body-clipping may be the only treatment required. Since many affected animals are aged, routine oral care and correction of dental abnormalities cannot be overemphasized. In addition, assessment of diet and incorporation of pelleted feeds designed specifically for older equids (e.g., senior diets) should be considered. Sweet feeds and other concentrates high in soluble carbohydrate are best avoided (unless that is all that horses will eat), especially when PPID is accompanied by concurrent glucose and insulin dysregulation. Affected equids may also need to be separated from the herd if they are not getting adequate access to feed. Unfortunately, because the ventral abdomen may become somewhat pendulous, weight loss and muscle wasting in more severely affected animals may not be well-recognized by owners. Consequently, regular measurement of body weight (weight tape) and assessment of body condition score are important parameters to monitor during treatment.

Since the major musculoskeletal complication of PPID is chronic laminitis, regular hoof care is essential. It is important to emphasize to clients that medical treatment for PPID (pergolide) is not a direct medical treatment for laminitis, as the painful gait and hoof abscesses that can accompany chronic laminitis may persist, due to damage to the laminar bed that has already been sustained. Thus, intermittent use of non-steroidal anti-inflammatory drugs may be necessary. Although flare-ups of chronic laminitis remain a reason for euthanasia in PPID-affected equids, it also warrants emphasis that medical treatment of PPID combined with regular hoof care and management of glucose and insulin dysregulation can lead to substantial improvement in this complication. Further, because many PPID-affected patients may have secondary infections (e.g., sinusitis, dermatitis, and bronchopneumonia), intermittent or long-term administration of antibiotics, typically a potentiated sulfonamide, may be necessary in some cases. Finally, horses with PPID have also been shown to have a more rapid rise in fecal egg counts following anthelmentic administration, in comparison to normal, aged horses. Thus, attention to parasite burden by monitoring fecal egg counts and implementing appropriate anthelmentic practices should warrant greater attention in PPID-affected equids.

Medications for treatment of PPID: Medications that have been used to treat equids with PPID include serotonin antagonists (cyproheptadine), dopamine agonists (bromocriptine and pergolide), and trilostane, an inhibitor of adrenal steroidogenesis. Cyproheptadine was one of the initial drugs used because serotonin had been shown to be a secretagogue of ACTH in isolated rat pars intermedia tissue and because the medication was available at a reasonable cost. Early reports that cyproheptadine (0.5-1.0 mg/kg, PO, q 24 h) resulted in clinical improvement and normalization of laboratory data within 1-2 months have been disputed as similar clinical improvement has been achieved with improved nutrition, preventive care, and management alone. Further, two studies comparing both clinical improvement and endocrine test results have clearly shown that pergolide is more effective than cyproheptadine as monotherapy for treatment of PPID.

Because loss of hypothalamic dopaminergic innervation appears to be an important mechanism for development of PPID, treatment with dopaminergic agonists is a logical approach to therapy. Pergolide, a first generation dopamine agonist used for treatment of Parkinson's Disease (PD), was found to acutely lower plasma concentrations of immunoreactive adrenocorticotropin (ACTH) and other pro-opiomelanocortin peptides in an early report. Subsequently, pergolide treatment produced clinical improvement in 23 of 25 PPID-affected equids; however, the dosage was quite high (6-10 µg/kg, PO, q 24 h [3-5 mg to a 500 kg horse]) and the expense of treatment precluded routine use of the drug. When Peters and colleagues (1995 AAEP Convention) subsequently reported that using a lower dose of pergolide (2 µg/kg, PO, q 24 h [1 mg/day for a 500 kg horse]) was clinically effective in a series of horses and ponies with PPID, use of pergolide became more widespread as cost was no longer prohibitive. Reported adverse effects of pergolide include anorexia, diarrhea, and colic; however, the latter problems are more often associated with higher doses of the drug. Usually, only transient anorexia is recognized during the initial few weeks of "low dose" pergolide treatment and can be

overcome by stopping treatment for a few days and starting back at half the dose, slowly increasing to the desired dose. An occasional equid appears to abhor the taste of pergolide, no matter what formulation is provided. In the author's experience these equids are challenging and may never be able to be treated with pergolide. Although pregnant mares have been treated with the drug, safety of pergolide use during pregnancy has not been studied in equids. Many pregnant mares treated with pergolide have been anecdotally reported to deliver healthy, term foals and produce adequate milk. Consequently, it does not appear that discontinuation of pergolide treatment prior to foaling is warranted unless udder development does not appear to be progressing as expected prior to expected parturition date.

Limited information exists on pharmacokinetics of pergolide although the initial study performed reported plasma concentrations of the drug that were 4-10 times greater in horses than in humans after administration of a similar oral dose (10 µg/kg), suggesting greater bioavailability in equids. The authors of that study concluded that a daily dose of 1-2 µg/kg (0.5-1 mg to a 500 kg horse) would be expected to produce drug levels in equids similar to therapeutic plasma concentrations in humans with PD, yet twice-daily administration would more likely provide sustained plasma concentrations of the drug. More recent pharmacological studies have yielded conflicting results with pergolide half lives of 5.6 and 24 h reported. Another recent study found no difference in the decrease in plasma ACTH concentration between once or twice daily pergolide dosing. Consequently, the question of the "best" dosing interval remains unresolved at present, although once daily dosing seems to produce adequate clinical improvement in most PPID-affected equids.

Until 2007, pergolide had been available in tablet form (0.25-1.0 mg, Permax™, Eli Lilly) with this formulation costing $75-100/month for a treatment dose of 1 mg/day. Because this was not an inconsequential expense for many retired family pets, several compounding pharmacies started to market pergolide products as suspensions, granules, or even in treats, often at a cost that was less than half that of Permax™. In 2002, reports started to appear describing development of valvular heart disease with significant regurgitation in human patients that had been receiving long-term pergolide for treatment of PD. This complication ultimately led to voluntary withdrawal of Permax™ from the marketplace in 2007 and left compounding pharmacies as the only source of pergolide for PPID-affected equids. Unfortunately, there is limited regulatory oversight of compounding pharmacies and independent analysis of pergolide products from several compounding pharmacies revealed considerable variation in potency as well as degradation, especially of water-based drug suspensions, after as little as 2 weeks of storage. Of interest, considerable variation in pergolide content was even found between different scoops of a compounded granular formulation taken from the same container.

As with many chronic diseases in the horse, specific nutrient supplementation and complementary or alternative therapies, including acupuncture and herb mixtures, have been advocated for equids with PPID. A product made from chasteberry has been one

of the more popular herbs used; however, a small field study demonstrated that this product was an ineffective treatment for PPID.

Prascend™ field efficacy study and extended use studies: Because there was both need and demand for a consistent, high quality pergolide product, an open field clinical efficacy study with the goal of having pergolide approved by the FDA for treatment of equids with PPID was designed. The study enrolled 122 equids (59 male, 63 female, 10-35 years, 137-623 kg, and 16 breeds) at eight sites. Equids were enrolled between 11/1/08 and 1/31/09 based on clinical examination and endocrine testing results. Animals were scored (0-3) for hypertrichosis, hyperhidrosis, polyuria-polydipsia, abnormal fat distribution, and muscle wasting. Inclusion criteria were a hypertrichosis score $\geq$1 and either a plasma ACTH concentration $\geq$50 pg/ml (radioimmunoassay) or failure of endogenous cortisol concentration to suppress (<1.0 µg/dl) 19 h after dexamethasone administration (40 µg/kg, IM). Treatment with pergolide mesylate (2 µg/kg, PO, q 24 h) was started within 7 days of initial evaluation. Animals were re-evaluated (clinical exam and endocrine testing) after 90 (n=113) and 180 days (n=111) of treatment. When endocrine test results remained abnormal at 90 days (n=47), the dose was increased to 4 µg/kg, PO, q 24 h. Treatment success after 180 days was defined as either normalization of dexamethasone suppression test results (<1.0 ug/dl) or a decrease in plasma ACTH concentration by 50% (or to <50 pg/ml when initial value was <100 pg/ml) and improvement by a score of $\geq$1 in at least one clinical sign. Treatment was also considered successful when the sum of clinical scores decreased by $\geq$3, regardless of endocrine test results. Treatment compliance and minor adverse events were reported by reviewing daily written entries in a standardized diary at 90- and 180-day evaluations. Adverse events requiring veterinary evaluation during interim periods were reported to study investigators within 24 h and further investigated to determine seriousness.

In all, 76% (86/113) equids were classified as treatment successes (two horses withdrawn by their owners between 90 and 180 days were categorized treatment failures). The remaining nine animals died (n=8) or were euthanized (n=1) due to worsening of pre-existing conditions (laminitis and dental disorders) or colic. After 90 days of treatment, 58% (66/113) had normal endocrine test results and clinical improvement. Both median scores of clinical signs and mean concentrations of ACTH and cortisol (following dexamethasone administration) decreased during the study period. Transient inappetance was the most common adverse event observed in 40/122 (33%) equids, mostly during the initial 30 days of treatment. Other adverse events reported included lethargy, colic, diarrhea, lameness, and weight loss in less than 10% of cases and it was unclear whether or not these events were related to use of the drug. There were 10 reports of laminitis during the study: seven were considered flare-ups of chronic laminitis and three were apparently new cases of laminitis. The results of the open field efficacy study clearly demonstrated that pergolide was effective in improving clinical signs of PPID; however, not all clinical problems may be corrected, specifically laminitis.

A group of 30 equids (28 horses and two ponies) that completed the clinical efficacy study at Michigan State University were subsequently enrolled in an extended use study in August, 2009. Most enrolled horses were re-examined after 24 and 36 months of pergolide treatment and these equids had continued to receive the same dose (either 2 or 4 µg/kg, PO, q 24 h) that they had been receiving at the 6 month end point of the initial study. After 2.5 years of treatment (spring, 2011), all owners reported ongoing clinical improvement and overnight dexamethasone suppression test (ODST) results remained normal in 79% of tested equids (19 of 24 equids). Four horses were not tested at this time and two horses were lost due to causes unrelated to PPID (one sudden death and one euthanasia for neurological disease). Of interest, six horses with abnormal ODST results after 3 and 6 months of treatment had normal ODST results after 2.5 years of treatment with no increase in pergolide dose. After more than 5 years of treatment (May, 2014) owners were satisfied with the remaining equids attitude and condition, although patients clearly aged during the extended use study. Of the 12 remaining equids tested in spring 2014, plasma ACTH concentration was <50 pg/mL in 9 animals (75%) and ODST results also remained normal in 75% of horses (9 of 12 equids). At present (fall 2018) 5 equids remain in the extended use study and of the 25 that were lost, 22 died or were euthanized for age-related disorders and only three were euthanized for recurrent laminitis, a problem attributable to PPID. To date, the results of the extended use study support that long-term treatment of equids with PPID with pergolide results in clinical improvement, normalization of endocrine test results, and owner satisfaction in a high percentage of cases. Further, equids with PPID can be maintained for several years on pergolide therapy without a need for a progressive increase in drug dosage.

Current treatment recommendations: At present, it is the author's recommendation that the initial medical treatment for equids with PPID should be pergolide at a dose of 2 µg/kg, PO, q 24 hours (1 mg/day for a 500 kg horse). If no improvement is noted within 30 days (depending on season as hair coat changes will vary with the time of year that treatment is initiated), the daily dose can be increased by 1-2 µg/kg (to 1.5-2 mg/day for a 500 kg horse) with reassessment after 30 days. The author typically increases pergolide to a total dose of 6 µg/kg (3 mg/day for a 500 kg horse). If only a limited response is observed at this dose of pergolide and endocrine test results remain abnormal, addition of cyproheptadine (0.5 mg/kg, PO, q 24 hours) to pergolide therapy has been effective in a limited number of cases.

It is important to recognize that the rate of clinical improvement is higher than that for normalization of endocrine test results. For example, in a treatment study performed by the author, 13 of 20 pergolide treated horses were reported to have improved clinically while only seven of 20 had normalization of endocrine test results. Thus, it is prudent to regularly measure blood glucose concentration and perform follow-up endocrine testing when managing equids with PPID. The author currently recommends measuring plasma ACTH concentration at least yearly (between December and June in horses in the northern hemisphere) in horses that appear to be stable and 30 days after a change in medication dose.

Prognosis: Once present, PPID is a lifelong condition. Thus, the prognosis for correction of the disorder is poor. However, PPID can be effectively treated with a combination of management changes and medications. Thus, the prognosis for life is guarded to fair. The author has followed several horses treated with pergolide for nearly a decade and has become convinced that the drug improves the quality of life but does not necessarily prolong life.

The decision about if and when medical treatment for pituitary pars intermedia dysfunction (PPID) should be pursued remains challenging and should be approached on a case-by-case basis. Certainly, all older equids should have a complete evaluation of overall health status, with a particular emphasis on dental abnormalities, nutrition, and potential laminitis. Addition of pergolide treatment to the overall management plan typically improves quality of life of PPID-affected equids but there is no evidence that medical treatment prolongs life. Further, although pergolide is commonly administered to older horses that develop “endocrinopathic” laminitis, no data exist to support that pergolide treatment has a beneficial effect on laminitis. Although some horses experience a transient period of decreased appetite when pergolide treatment is started, the treatment has minimal other adverse effects other than cost to the owner. If the cost of treatment was a few pennies a day, rather than a few dollars, many equids would likely be started on pergolide with advancing age. Although it would be logical to assume that “prophylactic” treatment with pergolide should limit or prevent develop of clinical signs of PPID, it warrants emphasis that data are not available to support use of pergolide in this fashion.

References/Suggested Reading

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