Therapeutics for Equine Endocrine Disorders

Andy E. Durham, BSc, BVSc, CertEP, DEIM, MRCVS

KEYWORDS

• Equine • Endocrine • PPID • EMS • Diabetes • Therapeutics

KEY POINTS

- Endocrine disease is commonly encountered in equine practice.
- Pergolide remains the most popular drug for treating PPID although some alternatives exist if required.
- Equine metabolic syndrome control requires compliance with strict management measures although these may be supplemented by medical therapy in some cases.
- Rarer endocrinopathies such as diabetes mellitus, diabetes insipidus, hyperthyroidism and critical illness-related corticosteroid insufficiency present some therapeutic options but are frequently challenging to manage.

Endocrinopathic causes of laminitis have attracted considerable research interest over the last decade alongside a parallel surge in caseload seen in general equine practice.[1,2] The justification for medical intervention in cases of pituitary pars intermedia dysfunction (PPID) seems to be relatively straightforward, in contrast with the potential danger that equine metabolic syndrome (EMS) cases are medicated as an easier alternative to implementing essential management changes. Such reliance on medical treatment of EMS cases is likely to fail unless administered alongside strict dietary and exercise management.[3] Indeed, dietary management may also play an important role in other rarer endocrine diseases, such as diabetes mellitus (DM) and diabetes insipidus (DI), but such recommendations are beyond the scope of this article.

PITUITARY PARS INTERMEDIA DYSFUNCTION

PPID is suspected to arise after a loss of dopaminergic neuronal input to the pars intermedia, thus freeing the secretory melanotrope cells from tonic inhibition.[4] This pathophysiology forms the basis for preferential selection of dopaminergic agents in PPID

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Liphook Equine Hospital, Liphook, Hampshire GU30 7JG, UK
E-mail address: andy.durham@theleh.co.uk

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cases to moderate excessive pars intermedia secretion.[5,6] There is currently no evidence that medical treatment (**Table 1**) can reduce or reverse the pathologic changes in the affected pars intermedia of PPID cases,[7] although this is a variable but realistic expectation in association with treatment of human prolactinomas with dopamine agonists.[8]

The dopamine agonist pergolide mesylate was first approved for the treatment of Parkinson's disease in humans more than 30 years ago and remains the only equine-licensed drug for the treatment of PPID in horses (Prascend, Boerhinger Ingelheim). The drug acts as a potent agonist of dopamine D2 receptors, but has additional effects on other classes of dopamine receptors as well as adrenergic and 5-hydroxytryptamine receptors. The drug was withdrawn as a human medicine from the United States and Canadian market in 2007 owing to increased risk of cardiac valvulopathy. Similar adverse effects are not recognized in horses, although temporary inappetence is not uncommon after commencement of medication or after dosage increases.[9,10] Pergolide is generally administered at a starting dose of 0.002 mg/kg orally (PO) every 24 hours with clinical and endocrine improvement expected within 1 to 3 months.[9–14] Improvements in signs such as lethargy, hypertrichosis, and polydipsia may be readily noticeable, although it is less easy to judge treatment success based on reduced likelihood of further attacks of laminitis or susceptibility to infections. Hence, there may be value in monitoring endocrine test results, although it should be stated that clinical and endocrine improvements do not always concur. Similarly, in human studies of prolactinomas, there may be poor correlation between clinical signs, prolactin concentrations, and adenoma size after treatment with dopamine agonists.[8] Unpublished data from this author (AE Durham, 2014) monitored endocrine changes between 1 and 2 months after the treatment of 402 PPID cases with 0.002 mg/kg pergolide every 24 hours. This revealed that 30% of cases showed a return of plasma adrenocorticotrophic hormone (ACTH) concentrations to the reference interval. A further 41% of horses showed a greater than 50% decrease in basal ACTH concentrations, but

Table 1
Drug dosages for PPID and EMS in horses

	Drug	Dosage	Comments
PPID	Pergolide	0.002–0.010 mg/kg PO q24h	Begin at lower end of dose range and increase gradually if required. Inappetence not uncommon.
	Cyproheptadine	0.25 mg/kg PO q12–24h	May be used alone or in combination with pergolide.
	Bromocryptine	0.1 mg/kg PO q12h	Alternative dopamine agonist to pergolide.
	Trilostane	0.4–1 mg/kg PO q24h	Only indicated if evidence of hyperadrenocorticism.
EMS	Levothyroxine	0.1 mg/kg PO q24h for 3–6 mon, then taper to 0.05 mg/kg PO q24h for 2 wk, then 0.025 mg/kg PO q24h for 2 wk	Must be used alongside dietary control.
	Metformin	30 mg/kg PO q12h	Ideally, immediately before grazing/feeding

Abbreviations: EMS, equine metabolic syndrome; PO, per os; PPID, pituitary pars intermedia dysfunction.

they failed to return to the reference interval. There was no notable change in post-treatment plasma ACTH in 11% of cases (**Fig. 1**), which is similar to the 15% nonresponse rate reported in pergolide treatment of prolactinomas in humans.[8,15]

The reason for variable responsiveness of treated cases is unknown but could relate to interindividual differences in pergolide pharmacokinetics/pharmacodynamics and/or an inherent variability in the exact nature of the disease process. PPID is clearly a heterogeneous disease with a spectrum from hyperplasia and hypertrophy to microadenoma and macroadenoma formation[16,17] and, intuitively, the dose–response might differ between these pathologic categories. Human studies of drug-resistant prolactinomas have indicated similar plasma dopamine agonist concentrations in responsive versus unresponsive patients,[18] although there is a significant decrease in dopaminergic D2 binding sites, as well as dysregulated intracellular transduction pathways, in the pituitary glands of the latter group.[15,19,20]

Gradual dosage increases are probably the most common approach in nonresponders to pergolide, with some horses eventually receiving doses as high as 0.01 mg/kg per day.[10] Pharmacokinetic studies of pergolide in horses are inconclusive[21–23] and although twice daily dosing has been reported,[24] there is no evidence of additional benefit versus once daily dosing.[25] Nevertheless this seems a reasonable approach to try in nonresponders because there is no apparent therapeutic disadvantage.[25] The final therapeutic tactic with pergolide in apparent nonresponders is patience, because it has been observed that good treatment responses can be delayed for as long as 3 to 4 years in some cases (H.C. Schott, personal communication, 2014).

Switching dopamine agonists has been shown to be another effective approach in several human studies of drug-resistant hyperprolactinemia, with a change to cabergoline seeming to be most successful.[26–28] The dopaminergic agonists bromocriptine and cabergoline have been used in horses, although neither drug has been extensively investigated in PPID cases. Bromocryptine is a selective D2 dopamine agonist with a shorter half-life than pergolide, but it has been shown to be effective in controlling PPID at a dose of 0.1 mg/kg PO every 12 hours.[29] Anecdotal reports exist of the use of cabergoline, an especially long-acting D2 receptor agonist, in PPID cases. This author is not aware of clinical studies of cabergoline in PPID cases, although pars intermedia responsiveness has been shown to be decreased in normal horses by administration of 0.01 mg/kg cabergoline intramuscularly every 10 days.[30]

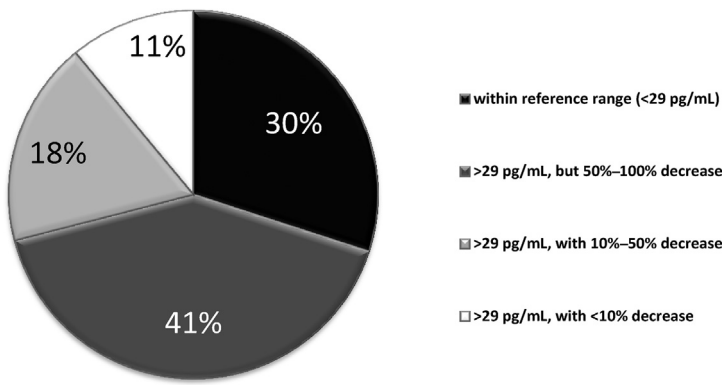

Fig. 1. Endocrine responses, judged by changes in plasma adrenocorticotrophic hormone concentrations, in 402 pituitary pars intermedia dysfunction cases after 1 to 2 months of pergolide treatment at 0.002 mg/kg orally every 24 hours (AE Durham, 2014).

Cyproheptadine hydrochloride is a further product with multiple modes of action, primarily listed as a serotonin, cholinergic, and histamine antagonist. The origin of its use in PPID likely lies in reports of decreased ACTH secretion from pars distalis corticotrophs in humans,[31] although there is no established mode of action in PPID cases. Reports have described inconsistent efficacy of cyproheptadine in PPID,[12,13,32] although the most favorable study used a higher dosage of 0.25 mg/kg every 12 hours.[12] Anecdotally, treatment responses have been reported in PPID using a combination of pergolide and cyproheptadine where 1 drug alone seemed to be ineffective.

Adrenal corticosteroid biosynthesis inhibitors have also been administered to PPID cases with favorable responses reported for trilostane, administered at 0.4 to 1.0 mg/kg PO every 24 hours.[33,34] Although increased basal plasma ACTH concentration is clearly associated with the presence of PPID,[35] the frequent absence of secondary adrenal hyperplasia and hypercortisolemia[36,37] suggests that most PPID cases do not suffer from hyperadrenocorticism, and that trilostane and similar drugs are unlikely to benefit the majority of cases.

EQUINE METABOLIC SYNDROME

EMS was initially recognized and named in recognition of analogy with the metabolic syndrome in humans,[38] although it is evident that there are also numerous fundamental differences between the 2 conditions. Key therapeutic targets in humans with the metabolic syndrome include hyperglycemia, dyslipidemia, atherosclerosis, pancreatic beta cell failure, and chronic hypertension, none of which seem to be real concerns in equids. Thus, although pharmacotherapy of the metabolic syndrome is practiced commonly, interspecies differences mean that caution should be exercised when considering similar drugs in EMS cases.

To apply effective pharmacotherapy, it is important to have a clear idea of the pathophysiologic processes that we wish to moderate. The primary clinical concern in EMS cases is laminitis, which is commonly pasture or diet associated. Two linked elements of probable fundamental importance are that several studies have indicated sustained hyperinsulinemia will trigger laminitis,[39,40] whereas others have indicated that EMS cases demonstrate an excessive hyperinsulinemic response to oral sugars.[41] The underlying characteristics of EMS cases that lead to excessive hyperinsulinemia are not yet understood fully. They may represent a combination of genetic and acquired factors influencing several steps, potentially linking grazing with laminitis (**Fig. 2**). Management strategies play a key role in influencing many of these steps such as pasture management (restricted grass access, grazing muzzles, dry lots, etc), feeding diets with a reduced percentage of nonstructural carbohydrates, and obesity control through exercise programs. However, pharmacologic opportunities also exist and may play a role alongside good management (see **Table 1**).

The origins of levothyroxine administration to obese equids probably began with the misconception that hypothyroidism was prevalent in this population. However, clinical hypothyroidism, if it exists in equids, is clearly extremely rare and plays no role in EMS.[38] Nevertheless, metabolic benefits may still be attributable to an increased metabolic rate associated with levothyroxine supplementation in the absence of deficient endogenous secretory function. Obesity seems to be a significant but reversible contributing factor to insulin resistance (IR),[42] which, in turn, promotes compensatory hyperinsulinaemia[42] (see **Fig. 2**). Several studies have indicated enhanced weight loss[43–45] and proportionate improvements in insulin sensitivity[43] by 16 weeks when normal horses were treated with levothyroxine. Chronic therapy with levothyroxine

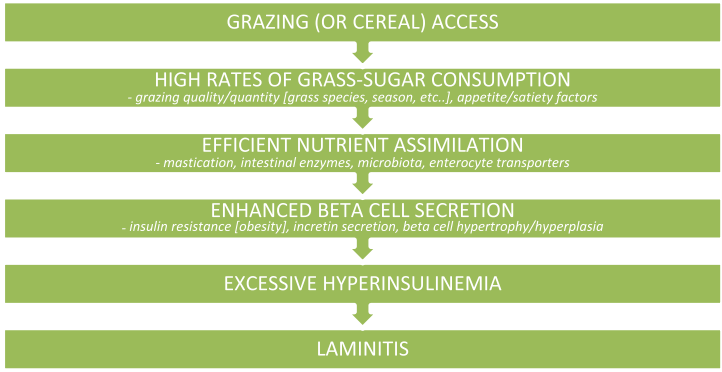

Fig. 2. Modifiable variables that might link grazing with predisposition to laminitis in individuals with equine metabolic syndrome.

has measurable cardiac effects as well as possible increased activity and mild hyperexcitability in treated horses, although none of the reported changes were judged to be of concern.[44]

In clinical practice levothyroxine sodium (Thyro-L, Lloyd Inc, Shenandoah, IA) may be indicated in individuals that seem to be particularly resistant to weight loss either owing to inherent metabolic characteristics[46] or perhaps owing to enforced exercise restriction as a result of chronic lameness. However, it is important that diet is controlled during treatment because an increased appetite may be a consequence of medication. A 3- to 6-month duration of treatment at a dosage of 0.1 mg/kg PO every 24 hours is recommended (approximately 48 mg [4 teaspoons] per day per 450–500 kg). A further increase in dosage by 50% (to 0.15 mg/kg) may be contemplated if there has been negligible impact on body condition by 3 months, although it is probably more important to closely scrutinize dietary management should this problem arise. When target body condition has been achieved, the dosage is decreased to 0.05 mg/kg for 2 weeks and then 0.025 mg/kg for a further 2 weeks before withdrawal to allow restoration of the suppressed thyroid axis.[45]

Unfortunately, commercially available levothyroxine products may be cost prohibitive in some countries, which has led to investigation of alternative pharmacologic aids for EMS. As a widely available, commonly prescribed, and affordable human generic product,[47] metformin hydrochloride was first used in a clinical study of EMS cases in the United Kingdom.[48] Given established modes of action in human subjects the authors of that study anticipated benefits in terms of improved insulin sensitivity, which was indeed consistent with the findings of decreased serum insulin and plasma glucose in metformin-treated subjects. However, further studies indicated very poor systemic absorption of metformin and no detectable effect on insulin sensitivity in treated horses,[49–51] leading to a revaluation of the drug's potential mode of action.[52]

Metformin hydrochloride is well-known to have multiple modes of action, although its insulin-sensitizing and antihyperglycemic properties dominate its description in humans,[53] a species in which the drug is highly bioavailable.[54] However, metformin is also recognized to have important presystemic pharmacologic effects on enterocytes, which are found to preferentially accumulate the drug after oral or intravenous administration without any prerequisite systemic absorption.[55,56] First in rodents[57] and subsequently in horses,[58] it has been shown that metformin significantly blunts the glycemic and insulinemic response to orally ingested sugars, a property with

potential therapeutic relevance to EMS given the proposed direct association of postprandial hyperinsulinemia with laminitis.[39,40] Interestingly, it seems that metformin paradoxically increases the uptake of intestinal luminal glucose through increasing GLUT2 expression on enterocyte brush border membranes, with the absorbed glucose being largely "wasted" by anaerobic glycolysis within the enterocyte.

Thus, it seems unlikely that metformin has any insulin-sensitizing effect, or indeed any other direct peripheral effects in horses. However, a decrease in enteric glucose absorption and the subsequent insulinemic response seems to be likely. This was first implied in the initial study of its use in EMS cases, which showed decreased blood concentrations of glucose and insulin after treatment.[48] Clinical benefits of metformin have not yet been investigated in treated horses, although at least 2 potential benefits exist. First, weight loss might be promoted by decreased glucose absorption as has been described in humans[53] and, second, moderation of postprandial hyperinsulinemia may reduce the likelihood of pasture-associated laminitis. Although both of these putative effects are intuitively beneficial in an individual prone to endocrinopathic laminitis, the ideal management of such horses should minimize dietary sugar content and grass access, thereby circumventing, or at least limiting, any possible beneficial effect of metformin.

It is important that clinical application of metformin should be considered in the context of the management and endocrine test results in the particular case. There may be a role for metformin where compliance with good dietary advice is compromised (eg, where owners insist on continued grazing), or perhaps as a longer term strategy in horses which have successfully lost weight but are found to retain an excessive insulinemic response to oral sugar tests. The dose regime for metformin is not currently established. The initial clinical study used a dose of 15 mg/kg PO every 12 hours and demonstrated a significant decrease in glucose and insulin concentrations.[48] A subsequent study demonstrating the enteric effects of metformin used a higher dose of 30 mg/kg PO.[58] Neither study cast any light on the duration of the drug's effects, although it is likely to be at least an hour.[58] In the absence of further pharmacokinetic data, where metformin is used to moderate postprandial hyperinsulinemia in horses, it seems appropriate to target the drug administration according to the timing of anticipated sugar ingestion; that is, administration immediately before turnout or feeding.

Thiazolidinedione drugs are commonly used in humans as insulin sensitizers, either alone or alongside other drugs such as metformin. These drugs activate a nuclear receptor called peroxisome proliferator activated receptor gamma, which regulates many genes involved in carbohydrate and lipid metabolism.[59] However, pioglitazone at 1 mg/kg PO attained relatively low plasma concentrations in horses[60] with little evidence of effects on insulin regulation[61] or inflammation.[62]

DIABETES MELLITUS

Occasional cases of DM are encountered in horses generally alongside signs of weight loss and polydipsia. Many cases of DM seem to be secondary to PPID,[35,63,64] although it is also reported in association with non–PPID-related chronic IR (type 2 DM)[63] and also primary pancreatic endocrine failure (type 1 DM).[65–68] Choice of therapy may depend on concentrations of endogenous insulin and the presence and degree of β-cell dysfunction, IR, and predisposing conditions such as PPID.

Attempted long-term treatment of equine DM cases with exogenous insulin therapy has generally proved both costly and disappointing. Type 2 DM cases have not responded well owing to the presence of marked IR,[69] but limited success has been

reported in cases of type 1 DM. Reasonable glycemic control was reported in a pony with DM secondary to pancreatitis treated with 1.0 IU/kg per day protamine zinc insulin as a single or divided dose administered intramuscularly.[66] Good clinical improvement was achieved over a 3-month period, although occasional hypoglycemic episodes arose. In a more recent case of type 1 DM in a horse, initial glycemic control was readily achieved with a constant rate intravenous infusion of 0.1 IU/kg per hour of regular insulin.[65] This was followed by long-term therapy using several different long acting insulins including Ultralente, Glargine, and Neutral Protamine Hagedorn at a dose of 0.4 IU/kg every 24 hours, with Neutral Protamine Hagedorn insulin seeming to be the most effective. Unfortunately, after 18 months, marked hyperglycemia recurred.

The effect of pergolide treatment on PPID-related DM is unclear. One study found that glucose concentrations did not change after pergolide treatment of PPID cases,[13] although other studies have demonstrated the contrary,[9] with 1 description of very prompt restoration of euglycemia within 12 hours of initiating pergolide treatment.[63] Despite apparently variable responses, it would seem advisable to at least attempt treatment with pergolide where PPID is identified in horses with DM. Other DM cases have been treated with insulin secretagogues in an attempt to regain glycemic control. Glyburide (glibenclamide) administration has been described in some reports[63,65,67] at up to 0.3 mg/kg PO every 12 hours. In the same reports, metformin was also administered, although given more recent evidence regarding the mode of action of this drug, including the absence of a peripheral insulin-sensitizing effect in horses (see above), it would seem unlikely to benefit equine DM cases.

DIABETES INSIPIDUS

Rarely, equine cases of polyuria and polydipsia as a result of DI are seen. Affected horses are essentially divisible into those failing to secrete vasopressin from their pituitary glands (central DI)[70,71] and those where their renal tubules fail to respond to vasopressin (peripheral DI).[72–74] Long-term pharmacologic treatment of equine DI cases is not reported, although several therapeutic options exist depending on which form is diagnosed.[75]

Only central DI cases are likely to be responsive to exogenous vasopressin therapy. This is usually in the form of desmopressin acetate,[76] but has only been reported as a short-term diagnostic measure in an equine case where a 10-mg dose administered as eye drops was effective in increasing urinary specific gravity in a 60-kg foal.[70] The anticonvulsant drug carbamazepine has been shown to have antidiuretic effects both through stimulation of central vasopressin release and by acting as an agonist of vasopressin receptors in the collecting ducts,[77] and may therefore be indicated in both central and peripheral DI. Its use or effectiveness in equid DI cases is unknown, although safety in horses is at least apparent from idiopathic headshaking cases.[78] Thiazide diuretics represent the main therapeutic modality for peripheral DI in other species.[79,80] These drugs decrease sodium (Na) and chloride (Cl) reabsorption in the distal convoluted tubule by inhibiting the Na–Cl cotransporter. The likely explanation for the paradoxic effect of reducing urinary output in DI cases is that increased Na losses lead to decreased extracellular fluid volume and decreased glomerular filtration rate, as well as increased Na and water reabsorption in the proximal tubule. Thiazides have not been reported in the treatment of equine DI, although hydrochlorothiazide (up to 3.3 mg/kg intravenously) is described for other purposes in horses.[81,82] Suspected central DI has been described in association with PPID in horses,[83] although the precise causes of polyuria and polydipsia in PPID cases are still not well-defined.[84] Nevertheless, attempted treatment of such cases with pergolide (or

cyproheptadine) would seem to be a reasonable initial approach as improvement in polyuria and polydipsia is described after treatment.[9,11–14] Additional therapeutic choices used in human DI cases include the antikaliuretic drug amiloride and renal prostaglandin inhibitors such as indomethacin, which increase water reabsorption and reduce polyuria,[75] although these are likely to be cost prohibitive in horses.

THYROID DISEASE

Although many cases of suspected equine hypothyroidism have been treated with levothyroxine replacement therapy, firm establishment of this diagnosis is not straightforward and serious doubts exist regarding its existence in adult horses.[38,85] Hyperthyroidism, although very rare, is less controversial and a few well-described cases are published.[86,87] Surgical treatment seems to be the favored approach, although a single report describes the additional medical treatment of one such case with propylthiouracil, an inhibitor of thyroid hormone synthesis, at a dose of 8 mg/kg PO every 24 to 48 hours.[88]

ADRENOCORTICAL DISEASE

Critical illness–related corticosteroid insufficiency describes a condition in which adrenocortical glucocorticoid secretory response is considered to be abnormally suppressed, and is a possible complication of and contributor to critical illness in humans and other animals.[89] The condition has been described in foals,[90,91] with 1 study suggesting that as many as one-half of hospitalized foals could be affected.[90,91] Glucocorticoid replacement therapy is described in foals using intravenous and oral prednisone,[90] with a more recent therapeutic proposal to administer hydrocortisone at 0.22 mg/kg intravenously every 4 hours.[92] However, considerable controversy still surrounds this condition in all species and diagnostic and treatment recommendations remain far from clear.[93,94]

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