Review Article

Pituitary pars intermedia dysfunction: Diagnosis and treatment

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Summary

Pituitary pars intermedia dysfunction is a common problem with which equine practitioners are becoming involved ever more frequently. This current review aims to outline recommendations for diagnosis, treatment and monitoring of the condition when encountered in practice.

Introduction

Pituitary pars intermedia dysfunction (PPID, equine Cushing’s disease) has evolved from a condition once regarded as a rare endocrinopathy of minority interest to practitioners, to a condition recognised almost daily in equine practice. Pituitary pars intermedia dysfunction is a prominent cause of morbidity in mature to elderly horses and ponies and may affect >20% of horses aged ≥15 years (McGowan et al. 2013a), although the disease is also seen in younger horses (Evans 1972; Orth et al. 1982; Heinrichs et al. 1990; Couëtil et al. 1996; Beech et al. 2011a). A recent study indicated a >12-fold increase in PPID admissions relative to total admissions in North American Veterinary Teaching Hospitals during the time period between 1993 and 2004 (Rohrbach et al. 2012). Recently a group of European medicine specialists produced a statement encompassing practical, evidence-based advice for equine practitioners when dealing with suspected PPID cases (Durham et al. 2013). A similar project has also been updated in the USA (Frank et al. 2013). This review serves to expand upon and update those statements and also includes data from several abstracts presented at recent specialist meetings (Durham and Copas 2011, 2012; Durham 2012; Gimpfinger and Fey 2012; Rendle et al. 2012; Schott et al. 2013).

Clinical signs

Early signs of PPID include laminitis, abnormal hair-shedding patterns, muscle atrophy leading to a ‘pot-belly’ and/or ‘wasted topline’ appearance, abnormal fat distribution (especially periorbital), and lethargy and should be regarded as potential signals of future, more serious clinical disease. Other signs that may be seen in association with PPID include hair colour fading or changing colour, polydipsia and polyuria, excessive or decreased sweating, susceptibility to secondary infections, infertility and, rarely, seizure-like activity (McFarlane 2011). Various clinical signs may trigger veterinary investigation of suspected PPID, with laminitis being the most serious, although by no means do all cases of PPID develop laminitis. It is likely that subclinical PPID has been present for months to years prior to development of clinically recognised laminitis. An Australian study showed a laminitis prevalence of 13% in 69 aged horses diagnosed with PPID, representing a 4.65 times odds ratio (95% confidence interval 1.50–14.4; P<0.001) compared with 256 controls (McGowan et al. 2013a). In comparison, higher laminitis prevalence rates of 24–82% have been reported in veterinary hospitals (Schott 2002; McGowan 2003).

Laboratory testing of PPID cases

Laboratory testing of suspected PPID cases is indicated both for confirmation of PPID and also to provide insight into the wider health status of the individual. Routine haematology and biochemistry are not useful in establishing a diagnosis of PPID although a general health screen and faecal worm egg count may be useful for identification of concurrent disease. Measurement of serum insulin and plasma glucose concentrations are also recommended (see later).

The presence of advancing age and clinical signs may be considered adequate for a clinical diagnosis in the field. However, laboratory testing is also of importance for several reasons including investigation of equivocal cases, subclinical cases, differentiation from equine metabolic syndrome (NB the conditions might coexist), for owners reluctant to start life-long treatment without strong evidence as well as for monitoring treatment efficacy.

Current diagnostic tests for PPID that are considered to possess adequate accuracy and availability for clinical use comprise basal plasma adrenocorticotropic hormone (ACTH) concentration, the overnight dexamethasone suppression test (ODST) and the thyrotropin-releasing hormone (TRH) stimulation test (measuring ACTH).

Basal plasma ACTH concentration

In normal horses physiological production of ACTH occurs in corticosterone cells in the pars distalis, which release the hormone in response to corticotropin releasing factor following cleavage from the parent peptide POMC. It is thought that in normal horses only about 2% of circulating ACTH is derived from the melanotrope cells of the pars intermedia as further cleavage normally results in conversion of ACTH into α-melanocyte-stimulating hormone and corticotropin-like intermediate peptide (Wilson et al. 1982). In PPID cases there is overproduction of immunoreactive ACTH from pars intermedia melanotropes (Orth and Nicholson 1982; Wilson et al. 1982).

Determination of the resting plasma ACTH concentration is the most practical diagnostic test for PPID, perhaps due to...
the simplicity of collection of a single sample and also the availability of seasonal reference ranges in some laboratories that allow testing at any time of year (Copas and Durham 2012). Although increased basal plasma ACTH concentration is clearly associated with the presence of PPID (van der Kolk et al. 1995), adrenal hyperplasia is frequently absent and plasma cortisol concentration is generally normal (McFarlane et al. 2006; Beech et al 2011b). This has been attributed to the finding that pars intermedia-derived immunoreactive ACTH in PPID cases is significantly less bioactive than the pars distalis-derived ACTH (Orth and Nicholson 1982; Sommer 2003; Beech et al. 2011b; Cordero et al. 2011).

Several in vivo and in vitro factors other than PPID could influence the measured concentration of ACTH. Variation in results from different analysers, at different times of year and in different geographic locations makes it important that individual laboratories establish reference intervals (Schott et al. 2012; Gehlen and Bradaric 2013). Further potentially important considerations are discussed below.

Seasonality
Donaldson et al. (2005) first noted that ACTH concentration in healthy horses and ponies was significantly higher when measured in September compared with January and May, indicative of an autumnal increase in pituitary activity and ACTH secretion, and advised avoidance of testing for PPID at that time of year. This circannual variability has been confirmed by other studies some of which established seasonal reference intervals, thus enabling year-round use of ACTH as a diagnostic test (Copas and Durham 2012; Gimpinger and Fey 2012). Copas and Durham (2012) further showed that the autuminal (August, September and October) increase in plasma ACTH concentration was even greater in horses with PPID than in normal horses indicating that responses to seasonal cues are not only retained but magnified in PPID (Fig 1). Consistent with this, another study demonstrated that the highest sensitivity and specificity of basal plasma ACTH concentration for PPID diagnosis was in the autumn using a seasonally adjusted reference range (McGowan et al. 2013b).

In vitro stability of ACTH
Adrenocorticotropic hormone is subject to in vitro degradation such that immunoreactivity decreases over time following sampling. Perkins et al. (2002) showed no significant decrease in measured ACTH when plasma was kept chilled for 8 h. Durham and Copas (2011) showed that when plasma was stored at 20–40°C there was a progressive decrease in measured ACTH but this was not significant until 3–6 h after storage, leading to advice that samples should be chilled within 3 h of collection and maintained in a chilled state until testing.

Protease inhibitors such as aprotinin and N-phenylmaleimide have been reported in non-equid species as an attempted means to increase stability of ACTH in vitro. Several equine studies have found that such products fail to prevent ACTH degradation and therefore they are not recommended (Bruns 2001; Durham and Copas 2011; Rendle et al. 2012).

Studies of delayed centrifugation of samples have indicated that unseparated whole blood or gravity separated plasma are suitable for testing as long as the samples are chilled promptly after collection and centrifuged upon receipt by the laboratory (Durham and Copas 2011). However, should a noncentrifuged or gravity separated sample become frozen then spuriously high ACTH concentrations will be measured, possibly as a result of cellular remnants carrying immunoreactive peptides (Durham and Copas 2011).

Timing of sampling
A few studies have looked into the possibility of diurnal variability in ACTH secretion and have generally found that, although some variability exists, it is not prominent and unlikely to affect diagnosis (Lee et al. 2010; Cordero et al. 2012; Rendle et al. 2012). However, ACTH concentrations may vary slightly through the day and therefore standardisation of sampling times is preferable when further samples are taken for comparison during monitoring.

Further possible short-term variability in ACTH secretion may occur as a result of pulsatile secretion in a small minority of cases although a single sample will generally be diagnostically acceptable. One study has also indicated that plasma ACTH concentrations are significantly lower after a 12 h fast than when measured 2 h after feeding at the end of the fast suggesting that diet may also need to be standardised when using this test for PPID investigation (Diez de Castro et al. 2013).

Stress/pain
Adrenocorticotropic hormone may intuitively be susceptible to variability as a result of the pain of laminitis, stress of transport or even any aversion to the blood sampling procedure. However, several studies have concluded that pain, stress and concurrent illness are only likely to affect diagnostic usefulness of ACTH when severe (Alexander et al. 1988; Couëtil et al. 1996). General anaesthesia, strenuous exercise, moderate to severe illness and severe pain may all increase plasma ACTH (Taylor 1989; Alexander et al. 1991; Towns et al. 2010) and where these conditions exist care should be taken in interpreting the result.

The above findings are condensed into general advice when using ACTH as a diagnostic aid for PPID (Table 1).

The diagnostic accuracy of plasma ACTH concentration has been subject to several studies. Van der Kolk et al. (1995) found perfect discrimination between 24 post mortem confirmed pituitary adenoma and 7 normal horses using a basal ACTH cut-off of 55 pg/ml (12.1 pmol/l) using
demonstrate increased ACTH concentration. However, some PPID cases may not require normal pituitary glands to have increased basal ACTH ranges were used. Thus it may be uncommon for horses with normal ranges for diagnosis of clinical PPID cases (McGowan et al. 2013b). In that study, the sensitivity and specificity were 80% and 82% respectively during the nonautumn months, and 100% and 95% in the autumn when seasonally adjusted reference ranges were used. Thus it may be uncommon for horses with normal pituitary glands to have increased basal ACTH concentration. However, some PPID cases may not demonstrate increased ACTH.

**TABLE 1: Advice for pretest handling of sample collected for ACTH analysis**

1. Collect EDTA plasma sample at any time of day (but be consistent if re-testing for comparison later)
2. Chill sample as soon as possible and within 3 h of collection
3. Centrifuge prior to shipping to laboratory (gravity separated samples can be shipped as long as they remain chilled and do not freeze)
4. Ship to laboratory using guaranteed overnight delivery in chilled packaging (freeze centrifuged plasma if delivery is delayed)

radioimmunoassay. Another series of publications, using chemiluminescent assay, comparing 13 post mortem confirmed clinical PPID cases vs. 22 normal horses indicated sensitivity for basal ACTH of 77% and specificity of 100% using a cut-off of 35 pg/ml (7.7 pmol/l), although test sensitivity was <50% when subclinical and mild clinical PPID cases were included (Beech et al. 2007; 2011a,b, personal communication). One study has looked at the sensitivity and specificity of basal ACTH using seasonally adjusted reference ranges for diagnosis of clinical PPID cases (McGowan et al. 2013b). In that study, the sensitivity and specificity were 80% and 82% respectively during the nonautumn months, and 100% and 95% in the autumn when seasonally adjusted reference ranges were used. Thus it may be uncommon for horses with normal pituitary glands to have increased basal ACTH concentration. However, some PPID cases may not demonstrate increased ACTH.

**ODST**

[Conversion factor for cortisol: μg/dl → nmol/l {×2759}; nmol/l → μg/dl {×0.362}]

In contrast to pars intermedia melanotropes, pars distalis corticotropes are subject to negative feedback from endogenous cortisol and administration of exogenous glucocorticoids leads to suppressed ACTH secretion. Thus, in the normal horse, where ACTH comes almost exclusively from the pars distalis, exogenous glucocorticoids are followed by a significant decrease in plasma cortisol concentration. However, in PPID, where significant quantities of ACTH are produced by the pars intermedia, cortisol secretion may be maintained in the face of administration of glucocorticoids (Dybdal et al. 1994).

The ODST might be favoured in some areas due to the widespread availability of cortisol assays and greater in vitro stability of cortisol vs. ACTH. Performance of the ODST requires veterinary attendance on 2 consecutive days presenting cost and time implications. Concerns also exist regarding possible adverse effects of dexamethasone administration in laminitis-prone individuals. Furthermore, ODST is subject to seasonal effects with false positive results likely in the autumn meaning that the test should not be used then (Donaldson et al. 2005; Schott et al. 2007). The procedure for the ODST is outlined in Table 2.

High cortisol concentrations 18–20 h following dexamethasone administration are indicative of PPID. Combination of 3 published studies (n = 111) comparing clinical PPID cases with normal horses, including post mortem confirmation of diagnosis and a cut-off of 27 nmol/l (10 μg/dl), indicated an overall test sensitivity of 89% and specificity of 88% (Dybdal et al. 1994; Frank et al. 2006; Beech et al. 2007). As with basal ACTH testing, ODST is likely to be less sensitive in subclinical or mild clinical PPID cases.

**TRH stimulation test**

Concerns regarding low sensitivity of basal ACTH and ODST for identification of PPID have provoked investigation of stimulation tests, especially for cases that might be in an early clinical or even preclinical phase. McFarlane et al. (2006) confirmed the presence of mRNA for TRH Type 1 receptors in both pars intermedia melanotropes and pars distalis corticotropes in normal and PPID horses. Administration of TRH in vivo leads to increases in plasma concentrations of ACTH and α-melanocyte-stimulating hormone in normal and PPID horses, although the response is significantly greater in PPID cases (McFarlane et al. 2006; Beech et al. 2007; 2011a,b). Plasma ACTH concentration peaks within 2–10 min of TRH injection and then gradually decreases back towards baseline by about one hour (Beech et al. 2007; 2011a,b; Funk et al. 2011) (Fig 2).

Thyrotropin-releasing hormone is not licensed for use in horses and owners should be warned that reactions to i.v. administration including transient muscle trembling, yawning, lip-smacking, flehmen and coughing are not uncommon (Beech et al. 2007). Supplies of TRH may be limited and costly in some areas, creating further problems with performing this test. The response to TRH is greater in the autumn months than at other times of year (Beech et al. 2007; 2011a,b; Funk et al. 2011) and, as no seasonal reference intervals are yet published, the test cannot be properly interpreted at that time of year. The recommended procedure for TRH stimulation testing is outlined in Table 3.

Currently the TRH stimulation test appears to offer higher diagnostic sensitivity compared with other tests for PPID (Beech et al. 2007; 2011a,b) and possibly offers the prospect of diagnosis at an earlier stage of disease. For diagnostic purposes, measuring plasma ACTH at 10 min post TRH is recommended using a cut-off of 110 ng/l, although the reference value might well be amended as greater numbers of test results are examined.

**Additional valuable tests**

The causal mechanism linking PPID with laminitis is unknown. Hyperinsulinaemia is well established as one of only a few proven causes of laminitis in horses and ponies (Asplin et al. 2007; de Laat et al. 2010) and insulin sensitivity is commonly decreased in association with PPID (Klinkhamer et al. 2011). Furthermore, McGowan et al. (2004) found that basal insulin concentration was negatively associated with prognosis in
PPID cases and Walsh et al. (2009) also found associations between laminitis and insulin concentration in PPID cases.

Hence, the measurement of serum insulin and glucose is strongly recommended in PPID cases as an indicator of laminitis risk, diabetes mellitus and prognosis. However, the conditions under which the tests are performed have a large influence on prevalence of abnormal results. Fasting hyperinsulinaemia is variably present in PPID cases although recent data have shown that most horses affected with PPID show an exaggerated insulinemic response to ingested glucose, suggesting that the insulin response to oral sugar challenge is more sensitive than basal insulin concentrations (Table 4). Despite logical concerns regarding the potential of oral sugar tests to provoke a hyperinsulinaemic capable of inducing iatrogenic laminitis, this is a consequence that appears to be extremely rare in the authors’ experiences.

**Treatment and monitoring recommendations**

The treatment of choice for PPID is pergolide mesylate (Prascend, Boehringer Ingelheim), which is licensed for use in horses. Use of other unlicensed drugs such as bromocriptine and cyproheptadine is reported although less supportive evidence exists (Beech 1994; Perkins et al. 2002). As PPID can vary from no clinical or mild signs and pars intermedia hyperplasia to prominent clinical signs and pars intermedia macroadenoma (Heinrichs et al. 1990; van der Kolk et al. 2004; Miller et al. 2008), it follows that required doses for control of PPID may vary between cases, in addition to possible inter-individual variation in bioavailability and drug action.

Treatment efficacy can be evaluated empirically after 1–3 months on the basis of clinical response including general attitude, increasing activity, start of hair shedding, improvement of laminitis and a decrease in water consumption if previously polydipsic (Pongratz et al. 2010; Rohrbach et al. 2012). However, monitoring changes in laboratory indicators of PPID may offer a more objective means of monitoring response to treatment. Several small studies have documented improvement in laboratory variables including basal ACTH and ODST response as objective markers of efficacy following treatment with pergolide or cyproheptadine (Peters et al. 1995; Schott et al. 2001; Donaldson et al. 2002; Perkins et al. 2002; Rohrbach et al. 2012). In one large study of 113 PPID cases following treatment with pergolide for 180 days, improvement in clinical signs and blood test results (basal ACTH or ODST) was observed in 76% of cases (Andrews et al. 2011).

Although consensus appears to favour a starting daily dose of pergolide of approximately 0.002 mg/kg bwt orally, the expected timing of detectable response to treatment has not been well defined. In one study 33 of 39 horses (85%) treated with pergolide following a diagnosis of PPID demonstrated a decrease of pretreatment plasma ACTH concentration to <35 ng/l and/or by >50% of baseline within a 3 month follow-up period. Of these 33 responding cases, only one (3%) had not responded by 28 days but did so later (Durham and Copas 2012). Therefore it is recommended that plasma ACTH is checked approximately 4 weeks following initiation of pergolide therapy or following dosage increases. However, treatment response can occasionally be delayed far longer than this perhaps reflecting more established and resistant pars intermedia pathology. Some PPID cases that initially fail to respond to pergolide treatment may eventually respond (as judged by clinical and laboratory tests) after as long as 3–4 years’ treatment (H.C. Schott, unpublished data).

Currently, for best practice it is recommended that the following protocol is used for management of PPID cases:

1. Document clinical findings. Obtain baseline clinical and endocrine values including baseline foot radiographs (even if laminitis is not clinically evident), and plasma ACTH, glucose and insulin concentrations or insulin response to oral sugar challenge (Table 4).
2. Owners should be encouraged to monitor appetite, hair coat, water intake and bed wetting when housed, body condition score, laminitis/lameness and general demeanour monthly.
3. Start pergolide at a dose of 0.002 mg/kg bwt per os q. 24 h (to the nearest 0.5 mg total dose; Table 5).
4. After one month of treatment, re-evaluate clinical signs, considering owner-reported changes, and endocrine values. One or more clinical signs is expected to improve and/or the basal ACTH to have returned to normal or close to normal range for that time of year (retest at same time of day and under same conditions as baseline values).
August, September and October using seasonally adjusted
confounding factor is suspected then retesting using the same
chilling) is important to improve test specificity. If no
in vitro
performed (e.g. stress, pain, sedation, lack of prompt
should be considered under such circumstances.

Discordance between results of different tests for PPID is well
described in cases with milder clinical signs and
intermedia
pathology. In one study, 21.5% of PPID cases had
recognised in cases with early/mild PPID) are often discordant with TRH stimulation
results whereas values
between 20 and 40 pg/ml (‘borderline’ results perhaps
representing a heterogeneous mix of normal horses and those
with early/mild PPID) are often discordant with TRH stimulation
results (Durham 2012; Rendle et al. 2014).

Plasma ACTH concentration fails to decrease significantly after pergolide therapy
Persistently increased plasma ACTH despite pergolide
treatment suggests ongoing pars intermedia dysfunction and
incomplete pharmacological control. If further increases in
pergolide dosage fail to improve the clinical and/or laboratory
findings then consideration could be given to using a different
drug such as trilostane or cyproheptadine. As these are
different classes of drug to pergolide they can be
administered alongside the pergolide therapy although
evidence for combined therapy remains scant. Given
evidence of some PPID cases that show drug responsiveness
several years after starting treatment as described above,
then withdrawal of treatment following apparent treatment
failure may be inadvisable and persistence might prove to be
helpful eventually. It is tempting to speculate that timing of
response may depend on pathology within the pars
intermedia with more established or progressed disease
requiring prolonged pergolide exposure before response is
seen.

A dilemma arises in cases where laboratory values fail to
improve despite apparent clinical improvement. However,
although it may be relatively easy to identify improvements in
many clinical signs such as attitude and haircoat, it may not
be so easy to identify clinically a decrease in future risk of
laminitis, in which case laboratory tests may be more
important (especially insulin – see below).

Serum insulin concentration remains increased
despite normalisation of ACTH or O DST
Several studies have indicated that most PPID cases treated
with pergolide and/or cyproheptadine demonstrate a
decrease in basal ACTH concentration and post-
dexamethasone cortisol (Peters et al. 1995; Schott et al. 2001;
Donaldson et al. 2002; Perkins et al. 2002; Andrews et al. 2011;
Rohrbach et al. 2012). However, measuring serum insulin may
have greater prognostic meaning (McGowan et al. 2004;

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<th>TABLE 4: Prevalence of hyperinsulinaemia in PPID cases according to test conditions (A.E. Durham unpublished data)</th>
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<td>Fasting hyperinsulinaemia (&gt;20 mU/l)</td>
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<td>Non-fasting hyperinsulinaemia (&gt;50 mU/l)</td>
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<td>Hyperinsulinaemia at 2 h after 1 g/kg bwt glucose (&gt;81 mU/l)</td>
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<th>TABLE 5: Suggested starting dosage of pergolide for treatment of PPID by bodyweight</th>
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5. If clinical and/or endocrine improvements are not noted,
increase the dose of pergolide by 0.001 mg/kg bwt.
6. Re-evaluate monthly with increases in the pergolide dose by
0.001 mg/kg bwt until clinical signs and endocrine
variables have improved or a maximal dose of
0.010 mg/kg bwt has been reached.
7. If signs of decreased appetite or worsening lethargy or
inactivity are observed; reduce the dose by increments of
0.001 mg/kg bwt and investigate for concurrent disease.
8. Once the signs have been successfully controlled, clinical
and endocrine monitoring can reduce to 2–4 times/year,
with at least one of these scheduled for between August
and October.
9. Owners should continue to monitor at least monthly
and alert their veterinarian if there is deterioration or
development of any new clinical signs.

Dilemmas arising during PPID management

Results from basal ACTH or O DST are in the ‘grey-zone’
Few clinical or laboratory tests produce entirely clear and
dichotomous positive or negative results and it should be
expected that in PPID investigation, as with most other
medical investigations, some results will create interpretative
difficulties. Interestingly original descriptions of basal ACTH
(van der Kolk et al. 1995) and O DST (Dybdal et al. 1994) for
diagnosis of PPID indicated 100% sensitivity and specificity
although it was likely that normal horses were compared with
those with advanced clinical disease in those early studies.
Discordance between results of different tests for PPID is well
recognised in cases with milder clinical signs and pars
intermedia pathology. In one study, 21.5% of PPID cases had
discordant results when tested with O DST and basal ACTH
(McFarlane et al. 2012). Intuitively, early and/or mild clinical
disease is likely to produce endocrine test results closer to the
laboratory reference interval cut-off and so further testing
should be considered under such circumstances.

Consideration of potential confounding factors for the test
performed (e.g. stress, pain, sedation, lack of prompt in vitro
chilling) is important to improve test specificity. If no
confounding factor is suspected then retesting using the same
test in 3–6 months might allow for some disease progression
and improve test sensitivity. Retesting basal ACTH during
August, September and October using seasonally adjusted
reference intervals is associated with higher test sensitivity than
testing at other times of year and increases the likelihood of
detecting PPID (McGowan et al. 2013b). Another option is to
retest using a different test. The TRH stimulation test is worthy of
consideration for this purpose as its sensitivity has been found
to be greater than that of basal ACTH or O DST.

Two studies indicate that, when applying a reference
interval cut-off of 29 pg/ml, basal ACTH concentrations
≤19 ng/l (‘clear negative’) and ≥39 pg/ml (‘clear positive’)
usually concur with TRH stimulation results whereas values
between 20 and 40 pg/ml (‘borderline’ results perhaps
representing a heterogeneous mix of normal horses and those
with early/mild PPID) are often discordant with TRH stimulation
results (Durham 2012; Rendle et al. 2014).

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Walsh et al. (2009) but this has not been subject to much examination following treatment of PPID. Where hyperinsulinaemia remains there may be ongoing risk of laminitis and further action is recommended. Andrews et al. (2011) described a significant decrease in mean basal insulin (and glucose) in 113 PPID cases following pergolide treatment from 70 to 43 mU/l although past treatment values were still commonly above the reference interval. A further study similarly indicated a decrease in median basal insulin from 48 to 18 mU/l (P<0.001) in 43 PPID cases within 4–8 weeks of starting pergolide. Interestingly, response in insulin was unrelated to response in ACTH concentrations (A.E. Durham, unpublished data).

Careful dietary control by restricting access to feeds high in nonstructural carbohydrates (e.g., cereals, high nonstructural carbohydrate pasture), which are likely to further increase insulin secretion is recommended in hyperinsulinaemic horses. However PPID horses should not be severely calorie restricted (unless obese) due to risk of exacerbating their catabolic status. If the horse is underweight, relatively high energy, noninsulinaemic feeds should be considered such as nonmalted sugar beet pulp, rice bran, alfalfa and vegetable oil. Adequate protein intake should also be ensured and ration balancers used where necessary. Exercise may be another means of improving peripheral insulin sensitivity and decreasing plasma insulin concentrations where absence of lameness from laminitis allows. Metformin has recently been shown to decrease glycaemic and insulinaemic responses to nonstructural carbohydrate ingestion in normal, insulin resistant and PPID horses (Rendle et al. 2013) and might also be considered alongside pergolide treatment in persistently hyperinsulinaemic cases. Safety and efficacy of metformin in diabetes mellitus cases has not been established to date (Durham et al. 2009).

Persistent laminitis

Persistent laminitis is frequently associated with failure to control the PPID and continued hyperinsulinaemia (Walsh et al. 2009). Rechecking basal ACTH concentration to see whether or not the pituitary gland remains dysfunctional despite treatment is recommended. Efforts should also be made to control serum insulin concentrations as discussed above. Additionally, appropriate farriery and digital support plays an important role in improving comfort in laminitis cases.

Inappetance

Poor appetite was described in 6/38 (16%) pergolide treated horses in one study (Pongratz et al. 2010) and in 40/122 (33%) in another (Andrews et al. 2011). Decreased appetite tends to occur within the first week after initiation of treatment or following dosage increases and is generally transient although can persist or recur. Initial gradual introduction of pergolide may decrease the incidence of inappetance in treated cases. Where inappetance is seen then the pergolide dose should be reduced or temporarily stopped, followed by a gradual increase again. It is also mandatory to consider alternative causes of inappetance and further clinical or clinicopathological investigations, especially dental and oral examinations are important.

Marked weight loss

Mild muscle wastage is not uncommon in PPID cases although more pronounced weight loss is deserving of further investigation. Andrews et al. (2011) reported weight loss in >50% of 122 treated PPID cases although this was only considered to be abnormal in 11/122 (9%). Further clinical or clinicopathological investigations are warranted in such cases, especially checking plasma and urine glucose for signs of marked hyperglycaemia and diabetes mellitus (Durham et al. 2009).

Conclusion

This review aimed to clarify and outline current thoughts on diagnosis and treatment of PPID in equine practice. Increasing interest in this common equine disease is likely to lead to further developments in our approach to such cases, perhaps most especially in the field of diagnostic techniques where room for further improvement clearly exists.

Diagnosis of PPID can be achieved using one, or a combination, of 3 highly specific laboratory tests. Sensitivity of testing remains a concern especially in nonautumnal testing of early or mild PPID cases. Adjunctive testing, especially examining for hyperinsulinaemia, is also recommended as a means of detecting cases at particular risk of laminitis. The cornerstone of management of PPID is use of pergolide mesylate (Prascend), although clinicians should be aware of the possibility of concurrent disease and manage accordingly.

Authors’ declaration of interests

No conflicts of interest have been declared.

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