Managing the endocrine aged horse with a focus on those at risk of laminitis

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Introduction

Aged and geriatric horses are becoming increasingly important in equine practice with referral hospitals documenting 5-10 fold increases in the proportions of geriatric patients over several decades. [1,2] This is due, in part, to better veterinary diagnosis and treatment options, but also is due to their owners presenting them for that care. Owners of aged horses are concerned about the health, welfare and quality of life of their aged animals, which is often due to a deep human-horse bond that has developed over many years of ownership. [3] Geriatric horses are owned for longer than younger horses [4] and surveys of management practices in epidemiological studies reflect a high level of owner dedication to these animals. [5,6] Pituitary pars intermedia dysfunction (PPID) is one of the more common geriatric diseases in horses, affecting over 20% of horses age 15 years and over, with an increasing prevalence with each subsequent year of age. [7] Although affecting older horses, veterinarians should be aware of the importance of their aged animals to many horse owners when planning management options for them. This in-depth review will discuss treatment and management of PPID, one of the most important diseases of aged horses, with a special focus on those cases with laminitis.

Initial Advice

Following a diagnosis of PPID, it is vital to fully inform the horse owner about the treatment options. Unlike the case a decade ago where conservative management was sometimes still advocated, medical treatment of PPID is now the accepted 'norm' and owners should have this option offered to them. As well as the availability of licensed medication, there is robust evidence supporting significant clinical and endocrinological improvements in more than three quarters of PPID horses that undergo treatment [8] and long-term improvements over many years have been maintained. [9]

During the initial explanation of the disease, it is important to ensure horse owners are aware of the disease and understand its basic pathophysiology and how the treatment works. A comparison with Parkinson's disease in humans or 'accelerated aging' may be the best way to explain it to owners, helping owners to understand why a medical therapy might be appropriate. McFarlane [10] suggests that the dopaminergic neurodegenerative process leading to PPID is associated with aging and has shown many similarities with Parkinson's disease in humans. The neurodegeneration causes a loss of dopaminergic inhibition of the pars intermedia of the pituitary gland [11]. The result is a loss of negative control of pars intermedia endocrine function and the overproduction of proopiomelanocortin (POMC) derived peptides produced by the pars intermedia melonotrope cells including adrenocorticotropin (ACTH), alpha melanocyte stimulating hormone (α-MSH), beta endorphin (β-endorphin) and corticotrophin-like intermediate peptide (CLIP). This overactive pars intermedia becomes hyperplastic on histological examination initially and in more advanced disease can become adenomatous, [12] but is not a primary tumor like owners may assume.

Treatment

Medical treatment of PPID involves daily oral administration of pergolide, a dopamine agonist, which is licensed (FDA approved) for use at a dose from 0.002 – 0.01 mg/kg PO q24h.[a] Treatment should be initiated at the low end of the dose range (to the nearest 0.5 mg) and gradually increased, if required, based on clinical and endocrinological response. [13]

Body Weight	Starting Daily Dose
200-350 kg	0.5 mg
350-600 kg	1.0 mg
601-850 kg	1.5 mg

Side effects

Although pergolide has few specific side effects, up to a third of treated horses will demonstrate transient inappetance on pergolide, and around 10% may appear dull or lethargic. [8] These side effects, especially inappetance, were more common when pergolide was first used at much higher initial doses. [14] Therefore, careful attention to gradual increases of the dose can reduce the occurrence of these side effects. If signs of inappetance or depression are observed, the dose can be reduced by increments of 0.001 mg/kg BW [13] or stopped for a short period (2-3 days or till appetite returns) and the dose restarted at half of the original dose. [15,16]

Interestingly, pergolide administered in target animal safety studies, depression and/or anorexia were not observed in normal horses, even at doses as high as 0.008 mg/kg for 6 months. [8] There were decreases in heart rate variably between geldings and mares, but only to the normal range. [8] Further research using normal horses in a blinded controlled cross over design trial using more detailed heart rate observations using holter monitor recording at rest, during stimulation and exercise did not demonstrate a difference in heart rate between groups. [17]

Despite the frequency of side effects, it is important to recognize that signs of inappetance of lethargy are non-specific and may accompany many diseases. Aged horses, even without PPID, have an increased risk of concurrent disease, [4] so on identification of these clinical signs, especially if they don't rapidly resolve with a reduction of dose, it may also be pertinent to investigate for concurrent disease.

Monitoring

Notwithstanding the improvements that most horses can expect from medical treatment, owners need to be aware that treatment is not curative, and medical treatment is a commitment that should be continued indefinitely, with monitoring, dose adjustments and ongoing care important parts of therapy. [13]

General health monitoring

Most horses with PPID will be in their 'teens' or older, with an increasing likelihood of diagnosis every year after 15 years of age.[7] Aged and geriatric horses have an increased susceptibility to a range of conditions and diseases, particularly dental disease (including periodontal disease), lameness, eye conditions, heart or lung conditions and skin conditions (including tumors such as sarcoids and melanomas). [4] PPID may increase the risk of intestinal parasitism [18] but does not alter a routine hematological or biochemical profile. [7] Despite an association between alterations in blood tests and PPID being reported, [16] it is important to note these have only been found in case series and not field based epidemiological research. [19] Case series rely on horses presented for veterinary care, and hence suffer from owner bias. As noted in the companion paper on this in depth session, epidemiological research has shown that many of the clinical signs of PPID are considered normal signs of aging by horse owners, including hypertrichosis and muscle atrophy, [20] so owners may inadvertently delay presentation for veterinary care until concurrent disease occurs. [19] Therefore, alterations in blood tests and concurrent illnesses should be investigated as concurrent disease, not ignored or presumed only associated with PPID.

In the aged population of horses presenting with PPID, there is a higher possibility of serious dental problems as well as periodontitis and diastema than younger horses [21] so dental work should be carried out with due veterinary care including sedation, pain relief and anti-inflammatory or other medication as necessary. If owners are fully informed of the high prevalence of these conditions in

their horses' age bracket and engage in regular health checks with appropriate blood testing, then the best outcomes can be achieved.

Monitoring clinical signs of PPID

Improvements in clinical signs are important monitoring tools and attention should be paid to trying to collect these as objectively as possible rather than just relying on endocrine 'numbers'. Body condition score (and muscle score), hair coat, demeanor, appetite, Obel grade of lameness if lame (or evidence of subclinical laminitis like laminitic rings, widened white line or dropped soles if not) and water intake can all be monitored. Baseline values should be obtained in consultation with the owner, then subsequently horse owners can be encouraged to monitor and record these e.g. monthly.

PPID endocrine monitoring

Endocrine monitoring should include both monitoring of PPID as well as monitoring for the risk of laminitis Testing for endocrine disease in the middle aged and older horse is covered in detail in a companion paper in this in depth session, but monitoring is achieved by repeating the endocrine testing used for diagnosis. For example, if basal ACTH was used for diagnosis, this value can be used as the baseline ACTH for follow up evaluation of response to treatment. The first follow up for a horse starting treatment for PPID should be within 4-6 weeks. [13,16] At this time ACTH values should have decreased substantially (e.g. by at least 50%) or be within the normal reference range, bearing in mind the seasonal increase in ACTH from late summer. [22,23] Although clinical signs may take longer to respond, most owners will detect an improved, brighter demeanor of their horse within this first time frame. [16] If clinical or endocrine improvements are not noted, increase the dose of pergolide by 0.001 – 0.002 mg/kg BW/day, to a maximum of 0.01 mg/kg. Each increment in dose should be monitored with follow-up assessments of clinical signs and endocrinological testing similarly (within 1-2 months) until the horse stabilizes. If clinical signs have stabilized for more than 3 months on a dose greater than 0.002mg/kg/day pergolide, a decrease of the pergolide dose by 0.001

mg/kg BW/day can be attempted, with the aim to reduce the dose back down to 0.002 mg/kg BW/day, bearing in mind that lower doses can result in treatment failure [13]

Once a suitable dose has been determined, follow up monitoring can decrease to 1 or 2 times a year. Where twice yearly monitoring is able to be performed, one of these follow up tests should be timed to occur during September when there is peak ACTH and maximal sensitivity for diagnostic testing, [23] bearing in mind the natural stimulation may push even a well-controlled horse a little outside of the seasonal reference range.

Monitoring for the risk of laminitis

In addition to monitoring PPID, it is also worthwhile measuring insulin dysregulation, either basally or dynamically, and this is imperative in horses with a prior history or current laminitis, including the presence of laminitic hoof changes. In horses with PPID, hyperinsulinemia is highly associated with laminitic lesions [25] and laminitis [7]. The presence of hyperinsulinemia is an important prognostic indicator for PPID survival overall [24] and the degree of insulin dysregulation provides a good indication of the risk of laminitis. Basal or dynamic (response to oral glucose or corn syrup) tests for hyperinsulinemia are recommended. [13,16] The timeframe for monitoring hyperinsulinemia can usually fit in with ACTH monitoring, but in some cases with poorly controlled laminitis, yet well controlled ACTH, it may need to be more frequent.

Management of the insulin dysregulated PPID horse (at risk for laminitis)

Insulin dysregulated horses should be managed to reduce hyperinsulinemia, but care should be taken not to treat exactly the same as horses with equine metabolic syndrome (EMS) without PPID. Prognosis is better in horses with controlled insulin dysregulation, even if this is unable to be completely normalized. [24] However, some advanced cases of PPID with insulin dysregulation can prove difficult to manage, even in the face of normalization of ACTH concentrations. In these cases, management of the insulin dysregulation using careful dietary control is advised.

Dietary considerations

Tailored dietary restriction and exercise has been shown to improve insulin dysregulation in horses with EMS [26] but can be less effective in horses with both PPID and insulin dysregulation. [27] In one study horses with both PPID and insulin dysregulation had a greater degree of insulin dysregulation and poorer response to dietary management than horses with insulin dysregulation only. [27] Horses with PPID are already at risk for muscle atrophy, most likely as a result of muscle catabolism [28] so dietary consideration should focus on the insulinemic response to feeds rather than on management of obesity and weight loss. In the author's opinion, even in obese PPID affected horses, weight loss should be carefully monitored and reductions of 0.25 – 0.5% BWT per week should be the maximum. Where persistent hyperinsulinemia exists, basally or dynamically, it is important to focus on the carbohydrate content of the diet, especially the non-structural carbohydrate content of the forage component which often forms the bulk of the diet.

Soaking hay is a good way to reduce water soluble carbohydrate content of hay and produces dramatic reductions in the insulinemic responses to forage in both normal and insulin dysregulated ponies (without PPID), [29] but soaking also results in leaching of water soluble minerals (especially sodium, chloride, potassium, calcium, phosphorus, magnesium and sulfur), [30] so careful attention to appropriate balancing of the diet is recommended. Similarly, although protein is not lost by soaking hay, [30] where horses are on a forage only diet where protein content can be marginal, careful attention to protein (especially high quality amino acid supplementation) and vitamin and mineral supplementation is important to prevent and reverse muscle loss and atrophy. [28]

In horses with more marked weight loss or unable to cope with long fiber, for example, due to dental disease, low glycemic short fiber or complete rations can be purchased. Higher fat rations provide a high density caloric source and tend to induce lower insulinemic responses when fed.

Further treatment

In some cases, pharmaceutical management such as metformin may help, although evidence supporting their effect on reducing hyperinsulinemia is limited [13] Exercise, where permitted due to concurrent orthopedic disease or laminitis is also useful to improver insulin dysregulation in horses with PPID.

Conclusions

PPID is an important disease of aged and geriatric horses. Although affecting older horses, veterinarians should be aware of the importance of aged animals to many horse owners when planning management options for them. There is now good evidence to suggest at least 75% of treated horses should respond to therapy, including advanced cases. Less advanced cases (and some advanced ones) can return to athletic function and even competition level activity, although competing on pergolide is still not allowed in many events so this should be checked before competition. Notwithstanding the improvements that most horses can expect from medical treatment, owners need to be aware that treatment is not curative, and medical treatment is a commitment that should be continued indefinitely. Monitoring and ongoing care are important parts of therapy. Monitoring clinical signs of PPID will help inform dose adjustments and monitoring for and treating concurrent disease will lead to optimal outcomes. Endocrinological monitoring for PPID is important to direct appropriate dose adjustments and endocrinological monitoring for insulin dysregulation will inform about the risk of laminitis and overall prognosis.

[a] Prascend, Boehringer Ingelheim

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