MANAGING EQUINE CUSHING'S

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Categories : Vets

Date : March 24, 2014

NICOLA MENZIES-GOW considers the options available in the management of this disease in horses, discussing the treatment of individual signs, which can improve quality of life

Summary

Not all owners will elect to treat pituitary pars intermedia dysfunction (PPID) specifically, depending on the clinical signs and how severe they are in an individual animal. The clinical signs can be managed individually – for example, clipping excess hair, treating infections, altering the diet to gain weight and treating laminitis. Where medical therapy is employed, the treatment of choice is the dopamine agonist pergolide (initial dose is 2g/kg po sid), which is licensed for the treatment of this condition in horses in the UK. It is reportedly effective in 65 per cent to 80 per cent of cases. The serotonin antagonist cyproheptadine does not appear to be any more effective than non-pharmacological management. The final drug that can be employed is the cortisol synthesis inhibitor trilostane (0.5mg/kg to 1mg/kg). It will only reduce the clinical signs associated with excess cortisol and its effectiveness is questionable. Normalisation of, or improvement of, endocrine tests can be used to monitor the response to therapy; alternatively, improvement in the clinical signs can be used. Lifelong drug therapy and/ or management of the clinical signs is required as all the available drugs will only help control the clinical signs, but not result in a cure. Despite this, many horses continue to have a good quality of life for a number of years.

Key words

pituitary, pars intermedia, Cushing's, pergolide, cyproheptadine, trilostane

THE pituitary gland is divided into two lobes, the anterior (adenohypophysis) and the posterior (neurohypophysis).

The anterior lobe is divided into the pars intermedia, the pars distalis and the pars tuberalis. The pars intermedia contains melanotropes that process the precursor hormone pro-opiomelanocortin (POMC) to produce mainly beta-endorphin, melanocyte- stimulating hormone (MSH) and corticotropin-like intermedia peptide (CLIP). Fewer than two per cent of the hormones produced by this area are adrenocorticotropic hormone (ACTH). Secretory control of the pars intermedia appears to be primarily through tonic inhibition by dopamine, with additional modulation by serotonin (5-hydroxytryptamine), beta-adrenergic and gamma-aminobutyric acid (or GABA-ergic) inputs. Dopamine in the pars intermedia is released directly from nerve terminals. The neurons originate in the periventricular nucleus of the hypothalamus. Dopamine released from these nerve terminals interacts at the D_2 receptors of the melanotropes to decrease POMC production.

Equine pituitary pars intermedia dysfunction (PPID) is a slowly progressive neurodegenerative disease with loss of dopaminergic (inhibitory) input to the melanotropes of the pars intermedia, which appears to be associated with localised oxidative stress and abnormal protein (alpha-synuclein) accumulation. The consequent dysfunction of this region results in hyperplasia of this area of the gland and overproduction of pars intermedia- derived hormones.

The condition is seen in older animals; the average age is 19 years. There is no breed or sex predilection, but ponies are more frequently affected than horses. Clinical signs include hirsuitism (hypertrichosis; Figure 1), weight loss, recurrent laminitis (Figure 2), polyuria and polydipsia, hyperhidrosis and lethargy. Diagnosis is based on signalment, clinical signs and further diagnostic test results.

There is no ideal further diagnostic test; but plasma basal ACTH concentrations and the cortisol response to a dexamethasone suppression test are the most appropriate initial tests. If the result of the test is inconclusive then the ACTH response to administration of thyrotropin-releasing hormone can be determined.

Treatment aims

PPID is a slowly progressive, lifelong condition. The aim is not to cure it, but to increase the quality of life by reducing the clinical signs, including those that have the potential to be life threatening.

Non-pharmacological management of equine PPID

Not all owners will elect to treat PPID specifically, depending on the clinical signs and how severe they are in an individual animal. The clinical signs can be managed individually:

- **Clip excess hair**

This will help with hypertrichosis and will also help with hyperhidrosis (excessive sweating) if it is secondary to the excess hair.

• Treat secondary infections

The specific treatment required will depend on the nature of the secondary infection. The most common secondary infections are gastrointestinal parasites, sinusitis and bacterial skin infections. Gastrointestinal parasitism will require appropriate anthelminthic therapy, depending on the specific parasite involved. Sinusitis should be treated initially with antibiotic therapy and appropriate adjunctive management changes, such as feeding from the floor to encourage sinus drainage. If this is not successful, further therapy such as sinuscopic lavage and standing sinusotomy may be required. Dermatological bacterial infections will require appropriate antibiotic therapy based on bacteriology results.

• Alter the diet to gain weight

The diet should ideally be analysed by a nutritionist and altered to promote weight gain through increased calorie consumption without increasing the risk of laminitis through excessive carbohydrate consumption.

• Treat laminitis

Laminitic episodes in animals with PPID should be treated in the same way as non-endocrinopathic laminitis. Therapy should be aimed at providing analgesia and foot support. NSAIDs given either orally or intravenously are the first choice for analgesia as they have the additional benefit of inhibiting part of the inflammatory cascade. There is no evidence to suggest any one specific NSAID is superior. If NSAIDs do not provide sufficient pain relief, then opiates can additionally be used such as butorphanol, pethidine, morphine and fentanyl patches.

Supporting the foot is an essential part of the management of acute laminitis. The horse naturally adopts a stance that bears most of the weight over the caudal part of the foot rather than the painful toe region. Additional support should be supplied to this region of the foot to provide pain relief and minimise the mechanical forces on the laminae and hence laminar tearing and pedal bone movement. The simplest method is to increase the depth of the bedding, ensuring it extends to the door where the horse will spend a significant proportion of its day standing. Shavings, sand, peat or hempbased products are best as they pack beneath the feet better than straw or paper.

Extra support can be applied directly to the caudal twothirds of the foot itself. This can be done in a variety of ways broadly divided into frog-only supports and combined frog and sole supports. Frog-only support can be achieved using rolled up bandaging material of the same length as the frog, placed along the length of the frog and secured in place with adhesive tape. Alternatively, a commercial product such as the Lily Pad or TLC Frog Support can be used. Combined frog and

sole support can be provided using, for example, dental impression material that is moulded to the contours of the caudal two thirds of the foot or Styrofoam pads that are crushed by the weight of the horse. No evidence suggests any one foot support method is superior.

The use of vasodilator or vasoconstrictor therapy in the treatment of laminitis remains controversial due to lack of knowledge of the pathophysiology of the disease. Vasodilator therapy is frequently used once the clinical signs have become apparent based on laminitis being a consequence of digital hypoperfusion. Acepromazine is the most effective digital vasodilator available. However, it should be acknowledged that even if the pathophysiology of laminitis involves vasoconstriction, this has normally resolved once the clinical signs become apparent. Nevertheless, the sedative effect of acepromazine may have the additional beneficial effect of reducing movement or even resulting in increased periods of time spent recumbent with the weight taken off the feet.

More recently, digital hypothermia or cryotherapy has been advocated. It has been shown to reduce the severity of lamellar injury and prevent lamellar structural failure when initiated at the detection of lameness in an experimental model of acute laminitis. However, it must be acknowledged the limbs were cooled using a rubber boot containing a mixture of 50 per cent cubed ice and 50 per cent water (constantly maintained over the 36-hour period) to a level just below the carpus, which may not be practical in the clinical setting.

Pharmacological management

Laminitis is the most common clinical sign that will enforce the use of pharmacological agents to help control the disease. Where specific medical therapy is used, there are three types of drug available.

Dopamine agonists

These drugs replace the lost dopaminergic inhibition to the pars intermedia and so reduce hormone production. Interaction with D_2 receptors inhibits hormone secretion and is therefore associated with improvement in clinical signs. It has not been determined whether pergolide treatment also inhibits the development of pituitary hyperplasia or reduces the size of pituitary adenomas, but these beneficial effects are plausible.

Pergolide is available as a product licensed in the UK for the treatment of PPID in horses (Prascend, Boehringer Ingelheim; **Figure 3**). It is reported to be effective in 65 per cent to 80 per cent of cases[1,2,3]. The initial dose is 2µg/kg po sid for four to six weeks. The dose is increased in increments of 1µg/kg/ day with reassessment every four to six weeks to a maximum of 6µg/kg/day if there is not adequate clinical response or decreased slowly at four-to-six-week intervals to the lowest apparently clinically effective dose.

Side effects include diarrhoea, depression, anorexia and colic, but only anorexia and depression

are reported with any frequency. If signs of dose intolerance develop, treatment should be stopped for two to three days and then reinstituted at half the previous dose. The total daily dose may then be gradually increased until the desired clinical effect is achieved, increasing in 0.5mg increments every two to four weeks. Contraindications to using pergolide include animals with a known hypersensitivity to pergolide or other ergot derivatives, animals under two years of age and pregnant or lactating animals.

PPID is a slowly progressive disease and the amount of pergolide required to control the symptoms is likely to increase as the horse ages. In addition, there is a normal increase in hormone production by the pituitary gland in the autumn. Some horses only seem to need pergolide during this seasonal rise in the early stages of the disease; alternatively, some horses appear to need an increased dose of pergolide during this seasonal rise.

The dopamine agonist bromocriptine is not used, as it is not adequately absorbed from the gastrointestinal tract.

Serotonin antagonists

Serotoni antagonists decrease the serotonin -induced stimulation to the pars intermedia. Cyproheptadine (0.25mg/kg to 0.5mg/kg po sid or bid; **Figure 4**) was used for the treatment of PPID and was reported to be effective in 28 per cent to 60 per cent of cases[1],[2],[4]. However, similar improvements were achieved with improved nutrition, preventive care and management alone[5]. In addition, pergolide has been shown to be more effective than cyproheptadine for the medical treatment of PPID[6]. Thus, cyproheptadine alone is no longer advocated for the treatment of equine PPID.

Cortisol synthesis inhibitors

Trilostane is a 3-beta hydroxysteroid dehydrogenase inhibitor. Thus, it inhibits cortisol production by the adrenal gland and so will only reduce the clinical signs associated with excess cortisol concentrations. In a single study, a dose of 0.5mg/kg to 1mg/kg sid was reported to be effective in 80 per cent of cases[7]. However, the improvement in the endocrinological results in this study was not convincing.

Complementary and alternative therapies

Alternatives that have been investigated include an aqueous extract of the herb *Vitex agnuscastus* (chasteberry), which is reported to contain compounds (diterpenoids) that stimulate dopamine D_2 receptor activity and inhibit different opioid receptors. Preliminary results of a study carried out by The Laminitis Clinic suggest it resulted in a reduction in depression (Eustace R, www.laminitisclinic.org), but there was no consistent effect on any of the other clinical signs associated with PPID and no trend towards normalisation of plasma concentrations of ACTH,

insulin or cortisol.

Therapeutic monitoring

It has been shown that of the horses receiving 1.5mg pergolide sid, which showed an improvement in their ACTH concentrations, 52 per cent to 72 per cent showed an improvement within seven days, 62 per cent to 82 per cent within 14 days and 74 per cent to 96 per cent within four weeks (www.thelaminitis site.org/ppid.html).

Thus, it is proposed the best practice for monitoring PPID includes measurement of plasma ACTH concentration 30 days after pergolide treatment is started. If it has not returned to within the seasonally adjusted reference range, then the dose should be incrementally increased (by 1µg/kg/day to 2µg/kg/day) at four-week intervals until it does. Once a suitable dose has been found, plasma ACTH concentrations should be measured annually, or some suggest biannually in the autumn and spring, and the pergolide dose adjusted to maintain plasma ACTH concentrations within the reference range.

Some horses have very high plasma ACTH concentrations and it may not be possible to return plasma ACTH concentrations to normal in these cases. Thus other approaches must be considered. Ideally, the dose should be incrementally increased to try to return plasma ACTH concentrations to within the reference range up to a maximum dose of 5mg sid. If finances preclude this approach, then an affordable dose that elicits a significant decrease in plasma ACTH concentration, even if concentrations remain above the reference range, should be used.

Alternatively, the clinical responses to treatment can be monitored in all cases. The clinical signs should be evaluated at 60 days following initiation of treatment. Outcomes of pergolide treatment include increased alertness and activity, resolution of polyuria and polydipsia, reduced incidence of laminitis, fewer bacterial infections, resolution of hyperglycaemia and hyperinsulinaemia, increased muscle mass and improvements in hair coat. Increased alertness and activity and decreased drinking and urination are reported to improve first, within 30 days; other signs may take several months to improve.

The dose of pergolide can be altered according to how well the clinical signs improve. Once the disease is controlled, regular clinical assessment should be performed every six months to monitor treatment success and the pergolide dose adjusted to maintain a clinical response.

Prognosis

The disease requires lifelong management and lifelong drug therapy, as all the available drugs will only help to control the clinical signs, but not result in a cure. However, many horses can continue to have a good quality of life for a number of years.

• Some of the drugs mentioned in this article are not licensed for use in equines.

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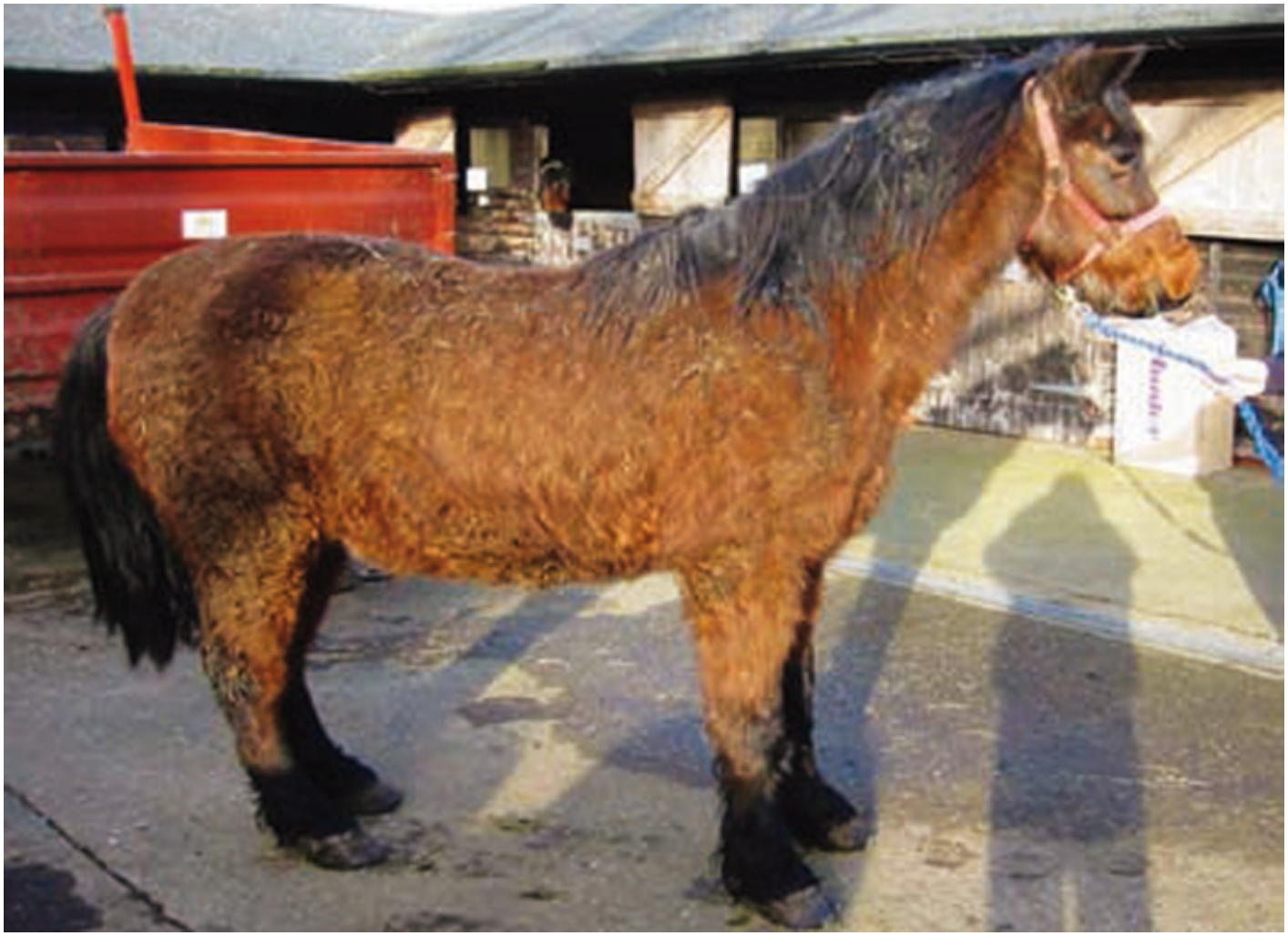

Figure 1 (top left). A 22-yearold New Forest pony mare with hypertrichosis characteristic of PPID.

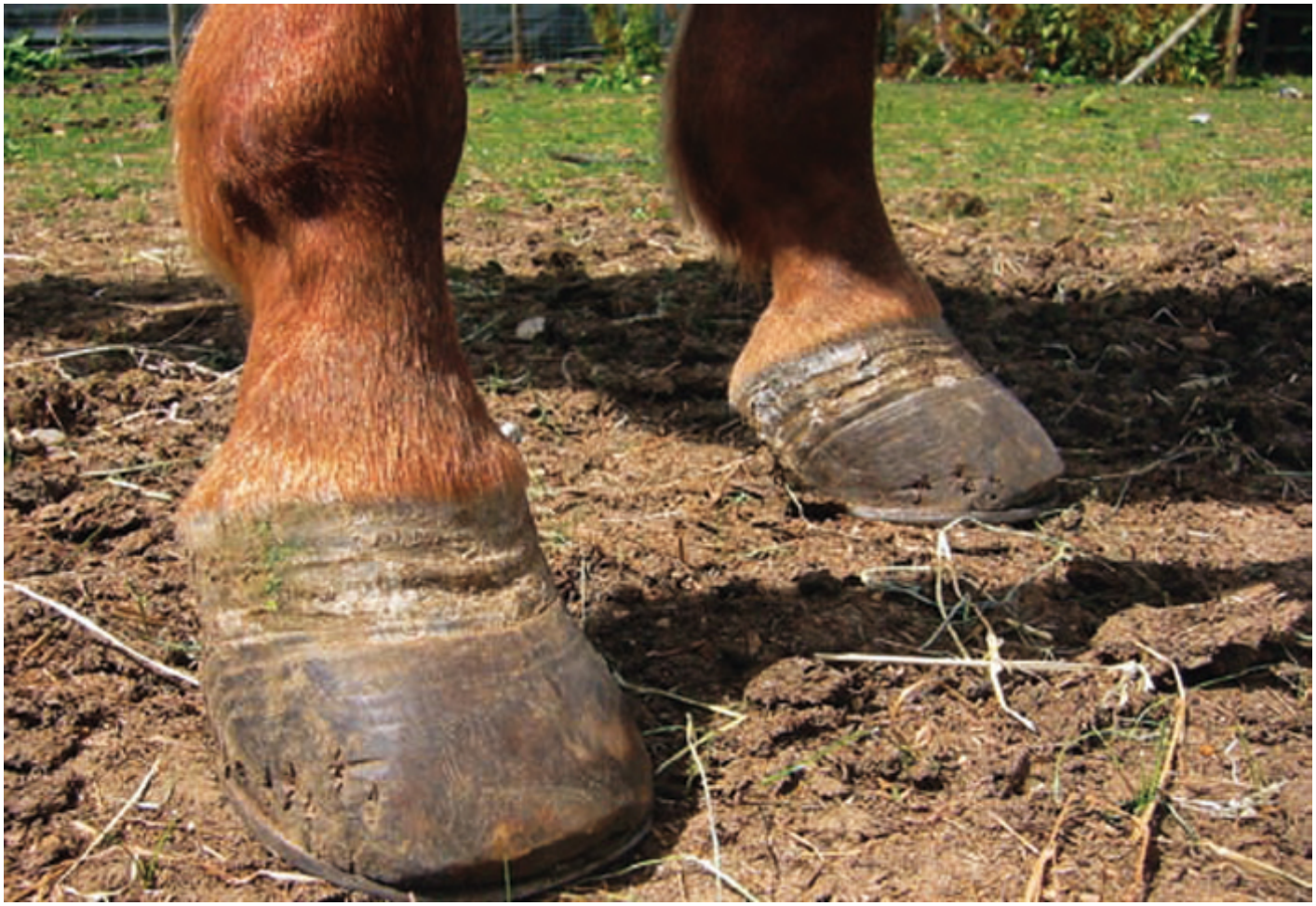

Figure 2 (below). Hoof changes consistent with recurrent laminitis.