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ORIGINAL RESEARCH

Pergolide dosing compliance and factors affecting the laboratory control of equine pituitary pars intermedia dysfunction

Natalie Hague[1] | **Andrew E. Durham**[2] | **Nicola J. Menzies-Gow**[1]

[1] Department of Clinical Sciences and Services, Royal Veterinary College, Hawkshead Lane, North Mymms, UK

[2] Liphook Equine Hospital, Liphook, Hampshire, UK

Correspondence
Nicola Menzies-Gow, Department of Clinical Sciences and Services, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire, AL9 7TA, UK.
Email: nmenziesgow@rvc.ac.uk

Abstract

Background: Equine pituitary pars intermedia dysfunction (PPID) is treated with daily pergolide therapy. Owner compliance and its effect on PPID control have not been previously investigated.

Methods: Clinical records were searched to identify the sample of animals with PPID treated with pergolide from 2016 to 2019. The signalment was noted and the dose of pergolide received calculated. Animals were classified as compliant (receiving ≥90% of the veterinarian recommended dose of pergolide) or non-compliant, and as controlled (follow-up basal adrenocorticotrophic hormone concentrations within the reference range) or not.

Results: In total, 110 animals were included. The majority (85%) were ≥16 years (mean ± SD 19.8 ± 4.4 years); the most common breeds were Cob (18%), Thoroughbred (16%) and Welsh (15%); 37% were female and 63% male. Overall, 48% were compliant and 52% non-compliant. There was no significant effect of compliance on laboratory control. Of those that were compliant, 74% were controlled, while 67% of non-compliant animals were controlled. Univariable analysis revealed a significant ($p < 0.001$) effect of age and breed on compliance and control, and of sex on control. On multivariable analysis, only age (compliance) and breed (compliance and control) were retained in the final model.

Conclusion: Only half of animals received the recommended pergolide dose; however, this did not affect laboratory control of PPID.

KEYWORDS
ACTH, compliance, control, pergolide, PPID

INTRODUCTION

In veterinary medicine, compliance describes the degree to which an owner correctly follows medical advice and most commonly it refers to medication or drug compliance. Medication compliance equates to the owner or person in charge administering the right medication, at the correct dose, by the correct route, at the right time, in the correct way, to the right patient.[1] Compliance is vital as it results in improved animal health and welfare. In human medical fields, drug compliance is frequently measured and rates average around 50%, although reports vary between 0% and 100%.[2] Compliance tends to be higher with more severe conditions and lower in perceived less important situations.[3] Veterinary data predominantly focus on dogs and cats and suggest similar short-term compliance rates of between 22% and 80%.[4–7]

Pituitary pars intermedia dysfunction (PPID) is a neurodegenerative disorder of the equine pituitary pars intermedia.[8] There is loss of the normal dopaminergic inhibition of this region of the pituitary by the hypothalamus.[9] Consequently, there is continuous stimulation of the pars intermedia melanotropes resulting in excessive production of their normal hormonal products derived from the cleavage of pro-opiomelanocortin including α-melanocyte stimulating hormone, corticotropin-like intermediate lobe peptide, β endorphin and adrenocorticotrophic hormone.[8] Over time, the continued stimulation results in melanocyte hypertrophy and eventually adenomatous change.[10]

Pergolide (Prascend; Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a dopaminergic agonist registered for the treatment of clinical signs associated with PPID in horses not intended for human consumption. Pergolide acts as an agonist for both the D_1 and D_2 receptors located on the melanotropes; receptor activation reduces hormone production by the pars intermedia and should therefore reduce clinical signs.[11] The treatment is aimed at controlling the clinical signs rather than curing the underlying disease, and lifelong therapy is required.[8] Treatment with pergolide is daily; hence the administration is the responsibility of the owner. Thus, it is possible that owners might forget on some days. Anecdotally, pergolide palatability has been reported as poor in some animals, dosing ponies under 150 kg accurately can be difficult as tablets have to be split.[12] As a result, owners may find dosing a difficult process and may not be giving treatment at the dose or the daily interval specified by the attending veterinarian.

There is no universal consensus with respect to what is considered to be a controlled case of PPID. Improvement of the initial clinical signs alone, reduction of the plasma ACTH concentration to within the seasonally adjusted reference ranges, or a combination of the two are all used to assess the control of PPID.[13,14] Improvement in the clinical signs can take up to 12 months and is based on the owner's subjective assessment, whereas normalisation of plasma ACTH concentrations is an objective measure of control that should occur within 4 weeks of commencing pergolide therapy in the majority of animals.[15]

The aim of this study was to determine the impact of owner medication compliance on the control of PPID defined as the return of plasma ACTH concentrations to within the seasonally adjusted reference interval in animals with PPID.

MATERIALS AND METHODS

This study was approved by the Royal Veterinary College (RVC) Social Science Ethical Review Board (URN SR2019-0051).

The clinical records from two first opinion equine veterinary practices, Liphook Equine Hospital and RVC Equine Practice, were searched to identify animals with PPID that were being treated with pergolide between 2016 and 2019. Animals were defined as having PPID if they had ≥1 clinical sign (hypertrichosis, lethargy, weight loss, recurrent laminitis, PU/PD) suggestive of PPID and a basal ACTH concentration above the seasonally adjusted reference interval at presentation. These animals were then included in the study if the amount of pergolide prescribed by the attending veterinarian was apparent from the clinical record, and follow-up measurements of basal ACTH concentration were recorded for at least 3 months. Clients who used a written prescription were excluded as it was not possible to determine how much pergolide was purchased. In addition, animals with multiple frequent changes in recommended dose or animals that had the dose changed due to the occurrence of side effects were excluded. The age, breed and sex of each animal were noted, and appropriate breed and age categories created. The dose of pergolide each animal received was calculated by dividing the amount of pergolide dispensed by the time period between each dispensing. Animals were classified as being compliant if they received an average dose of pergolide that was ≥90% of that recommended verbally to the owner by the attending veterinarian or non-compliant if they were receiving an average dose of pergolide < 90% of that recommended. Animals were classified as controlled if their follow-up basal ACTH concentrations were within the seasonally adjusted reference interval or not controlled if they were not. The reference interval used was previously established at the same laboratory used to perform the tests for the current study.[16]

Data analysis

The data were analysed using GraphPad Prism 7. The normality of the continuous data (age) was assessed using D'Agostino and Pearsons tests. The age data were then used to create categories (>12, 12–15, 16–20, 21–25 and >25 years). Individual factors significantly associated with compliance and/or control were initially determined using contingency table analysis. Significance was accepted at $p < 0.1$. Multivariable binary logistic regression with backwards-stepwise selection was then performed in order to determine the likelihood of these individual factors being associated with compliance or control, with only variables with $p < 0.05$ being retained in the final models. Interactions between risk factors were tested by calculating A*B for significant risk factors and entering A*B into the multivariable model. If the p value for the interaction term A*B was >0.05, there was no significant interaction between risk factors A and B, and they were sequentially on removed until all the risk factors had p values of ≤0.05 in the final model. The ORs and 95% CIs were calculated for significant variables.

RESULTS

In total, 110 cases were included in the study. The majority (85%) of animals were aged ≥16 years (mean ± SD 19.8 ± 4.4 years). Represented breeds were Cob and Cob crosses (18%), Thoroughbred (TB) and TB crosses (16%), Welsh and Welsh crosses (15%), other native ponies (11%), Shetlands (9%) and Warmbloods (6%). In addition, 37% were female and 63% male.

Overall, 53 of 110 (48%) were considered compliant and 57 of 110 (52%) non-compliant. Univariable analysis revealed that there was no significant effect of compliance on laboratory control. Of those that were compliant, 74% were controlled, and

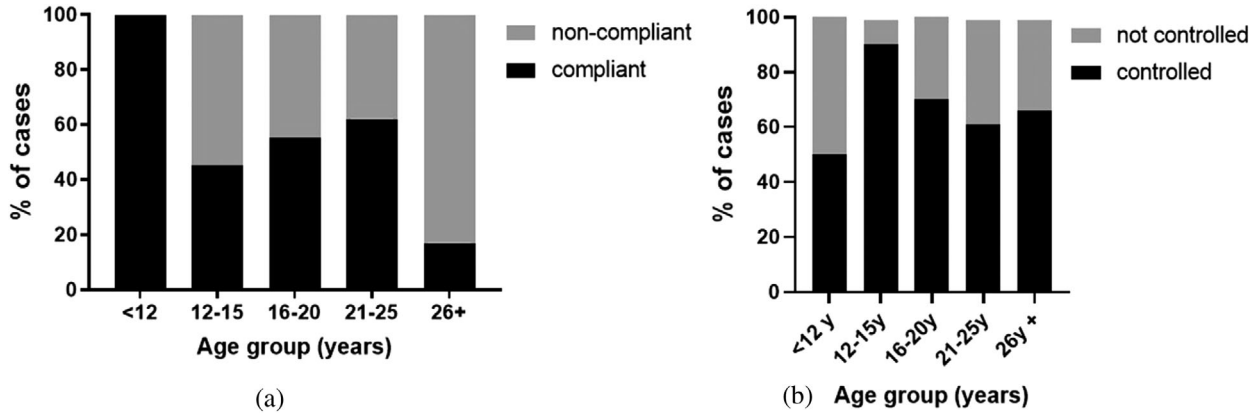

FIGURE 1 The effect of age on (a) compliance and (b) laboratory control in animals with PPID treated with pergolide

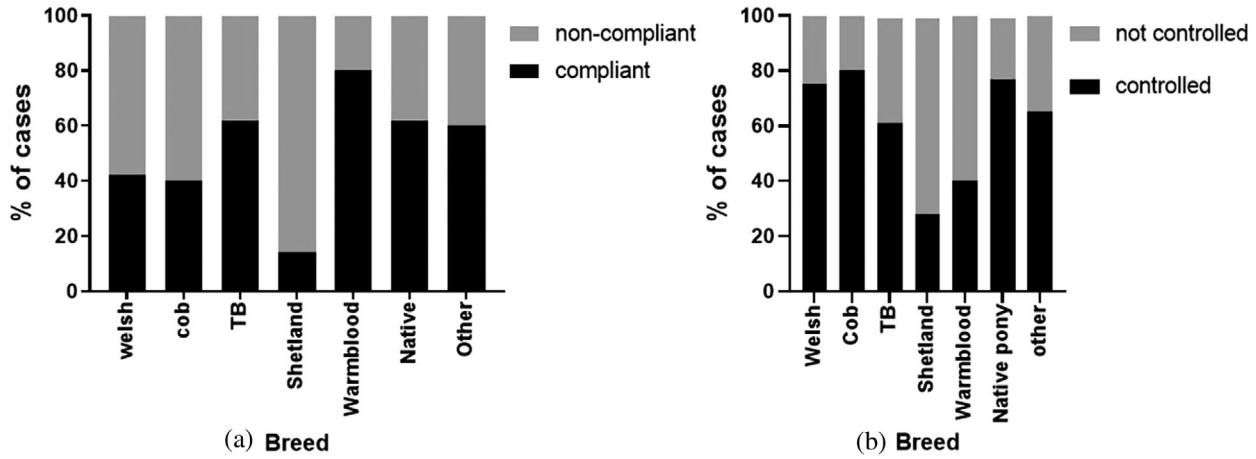

FIGURE 2 The effect of breed on (a) compliance and (b) laboratory control in animals with PPID treated with pergolide

26% were not controlled; while of those that were non-compliant, 67% were controlled, and 33% were not controlled.

On univariable analysis, there was a significant ($p < 0.001$) effect of age (Figure 1) and breed (Figure 2) on compliance and control, and of sex on control. Compliance was worst in the oldest age group of animals (≥26 years; 17% vs 57% in all other groups) and in Shetlands (14% vs 55% in all other breeds); while control was best in the 12–15 years group (91%) and in males (71% males were controlled compared to 63% of mares), and worst in Shetlands (29%).

Multivariable analysis confirmed a significant effect of age and breed on compliance (Table 1) and of breed on control (Table 2).

TABLE 1 Analysis of the variables retained in the multivariable model for compliance within horses treated with pergolide

Variable	OR	95% CI	p value
Age	0.53	0.30–0.93	0.03
Shetland	0.64	0.08–0.95	0.04

DISCUSSION

There is no universal consensus with respect to what is considered to be a controlled case of PPID. Improvement of the initial clinical signs alone, reduction of the plasma ACTH concentration to within the seasonally adjusted reference ranges set by laboratories and a combination of the two are all used to assess the control of PPID. For example, in some studies, there had to be an improvement in clinical signs or a normalisation of the laboratory data for an animal to be classified as controlled[13]; while in other studies, cases were classified as controlled based upon improvement in their clinical signs alone,[14] normalisation of the laboratory data alone,[17] or a ≥75% reduction in ACTH concentration.[17] In the present study, animals were classified as controlled based upon their plasma ACTH concentrations returning to within the

TABLE 2 Analysis of the variables retained in the multivariable model for control within horses treated with pergolide

Variable	OR	95% CI	p value
Shetland	0.18	0.04–0.93	0.04

seasonally adjusted reference range only, since it was not possible to accurately determine improvement in the clinical signs from the medical records. Thus, animals with significant improvements in their clinical signs and/or large reductions in their plasma ACTH concentrations may still have been classified as uncontrolled. In total, 70% of animals were classified as controlled, which is greater than previously reported studies in which 58% had normal endocrine test results after 90 days of pergolide treatment,[13] 40% had normal basal ACTH concentrations by the second recheck,[18] 30% showed a return of plasma ACTH concentrations to the reference interval 1–2 months after starting pergolide therapy[19] and 28% showed normalisation of basal ACTH concentrations.[17]

While there is conflicting evidence relating to whether breed is a risk factor for PPID,[20] the effect of breed on the laboratory response to pergolide therapy has not been reported. In the present study, Shetland ponies had the greatest proportion of uncontrolled cases. There are significant breed variations in plasma ACTH concentrations, with Shetland ponies having significantly higher plasma ACTH concentrations in September compared to other breeds.[21] This breed effect may have resulted in animals being misclassified as uncontrolled at this time of year, and seasonally adjusted references that are breed specific might be appropriate. In addition, it is possible that behavioural traits may make this breed more difficult to treat, and their small size may be a factor as they likely need to be treated with fractions of a tablet, and dosing accurately can be difficult when tablets have to be split.[12]

While there are several publications reporting medication compliance in small animals,[4–6] there is very little published research regarding compliance of horse owners with respect to medication dosing. In the single study that evaluated compliance in veterinary medication regimens for horses,[7] veterinarians significantly over-estimated the likelihood of clients being compliant, and horse owners were less likely to be compliant compared to companion animal owners (47% vs 55%). Furthermore, the study also found that horse owners were more likely to miss doses, give an incorrect dose or give the medication at the incorrect time compared to companion animals.[7] In a study that investigated horse owner compliance with respect to an environmental protocol recommended for the control of severe equine asthma, there was similarly poor compliance in 51.3% of the cases.[22] These results are similar to the compliance findings from the present study in which 48% of animals had compliant owners.

In the present study, there was a significant effect of age and breed on owner compliance; compliance was worst in animals aged ≥26 years. There is evidence to suggest that the frequency with which routine procedures such as vaccination and anthelmintic administration are carried out is reduced in geriatric animals.[23–26] Thus, it is possible that owners become being less committed to accurate lifelong therapy in aged animals resulting in reduced compliance. Compliance was worst in Shetlands. This may be due to the difficulty of having to split tablets in smaller animals; however, this is purely speculative.

Clients frequently have a very strong pet bond, and owners essentially want the best possible care for their animals, but they need to be involved in that initial decision making process and communicated regularly to be sure of compliance.[27] The recommendations need to include not only verbal, but also visual and/or written information. Secondly, compliance can be improved through advance scheduling of regular follow-ups and sending reminders[27] as owners are busy with life and are likely to forget or postpone their pet care responsibilities. Finally, compliance can be improved by establishing standard protocols for common conditions and then training the veterinary team to deliver a consistent message in an effective manner.[27] It is vital that equine veterinarians see the value in compliance and the steps that should be taken to maximise it as non-compliance has a negative impact on the animal due to prolonged recovery or failure to recover and on the owner due to dissatisfaction.

Surprisingly, there was no significant effect of compliance on the laboratory control of PPID in the present study. It has been demonstrated that there is a rapid response to treatment with pergolide, with a significant reduction in plasma ACTH concentration occurring 1 day after initiating therapy, followed by further smaller reductions over time.[28] This rapid reduction may help to explain the lack of a significant effect of owner compliance on control of plasma ACTH concentrations. A lapse and resumption of dosing by the owner, perhaps prompted by the return visit of the veterinarian, may not negatively impact on monitoring blood tests, therefore the horse would have been classified as controlled. In addition, the sensitivity and specificity of basal ACTH concentrations to make a diagnosis of PPID are such that a false positive diagnosis may occur.[29] In one study 70% of ponies classified as positive for PPID based on basal ACTH concentrations in the autumn were then categorised as PPID negative in the spring despite not receiving medical treatment for PPID.[30] Thus, it is possible that animals may have been misclassified at diagnosis or that plasma ACTH may have reduced to within the reference range regardless of the pergolide therapy in some individual animals included in the present study. Finally, animals had to be receiving ≥90% of the pergolide dose recommended by the veterinarian to be considered as compliant. It is possible that less than 90% of the recommended dose was sufficient to result in laboratory control in some animals.

The limitations of the present study include the fact that the information relating to the dose of pergolide prescribed for each animal was obtained from their clinical records. As with all retrospective case studies, the accuracy of this information is entirely dependent on the detail that is inputted by each individual veterinarian. Thus, it is possible that some details relating dose discussed during telephone calls or informal conversations were not always recorded. The compliance

was based entirely on the amount of pergolide being dispensed, and it is possible that the individual animals did not actually receive the medication or that the owners were obtaining medication from alternative sources without a prescription from the two veterinary practices included in the study. Finally, different equine veterinarians or veterinary practices may differ in their client communication and routine monitoring of PPID cases which in turn may lead to difference in owner compliance at medication regimens.

In conclusion, more than half of the animals included in this study did not appear to be receiving the dose of pergolide recommended. Thus, in the event of treatment failure, rather than simply increasing the dose prescribed, it would be prudent to investigate owner medication compliance and advise on how to overcome any barriers. While 70% of animals were considered to be controlled, and there was a significant effect of breed on this and of breed and age on owner compliance with respect to pergolide dosing, surprisingly there was no significant effect of compliance on control. Further studies evaluating the factors that affect horse owner medication compliance and methods that can be employed to improve it are warranted.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ORCID

Nicola J. Menzies-Gow https://orcid.org/0000-0002-3803-8069

REFERENCES

1. Cramer JA, Roy A, Burrell A. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44–7.
2. Nieuwlaat R, Wilczynski N, Navarro T. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;2014(11):CD000011.
3. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: a meta-analysis. Med Care. 2007;45(6):521–8.
4. Adams VJ, Campbell JR, Waldner CL, Dowling PM, Shmon CL. Evaluation of client compliance with short-term administration of antimicrobials to dogs. J Am Vet Med Assoc. 2005;226(4):567–74.
5. Barter LS, Maddison JE, Watson AD. Comparison of methods to assess dog owners' therapeutic compliance. Aust Vet J. 1996;74(6):443–6.
6. Barter LS, Watson AD, Maddison JE. Owner compliance with short term antimicrobial medication in dogs. Aust Vet J. 1996;74(4):277–80.
7. Verker JM, van Stokrom M, Edenburg N. How can veterinarians optimize owner compliance with medication regimes? Eur J Companion Anim Pract. 2008;18:73–7.
8. McFarlane D. Equine pituitary pars intermedia dysfunction. Vet Clin North Am Equine Pract. 2011;27(1):93–113.
9. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. Equine Vet J. 2013;45(1):74–9.
10. Glover CM, Miller LM, Dybdal NO, Lopez A, Duckett WM, McFarlane D. Extrapituitary and pituitary pathological findings in horses with pituitary pars intermedia dysfunction: a retrospective study. J Equine Vet Sci. 2009;29:146–53.
11. McFarlane D, Banse H, Knych HK, Maxwell LK. Pharmacokinetic and pharmacodynamic properties of pergolide mesylate following long-term administration to horses with pituitary pars intermedia dysfunction. J Vet Pharmacol Ther. 2017;40(2):158–64.
12. Rendle DI, Frost R, Byrne A. Efficacy of a novel palatable pergolide paste formulation for the treatment of pituitary pars intermedia dysfunction (PPID) in ponies. Equine Vet J. 2018;50(S52):16.
13. Adams AA, Siard MH, Reedy SE, Little JP, Grubbs S, Little MP. Does Equine Pituitary Pars Intermedia Dysfunction (PPID) Affect Immune Responses to Vaccination?. Paper presented at Dorothy Russell Havemeyer Foundation Equine Geriatric Workshop II and 3rd Equine Endocrine Summit; 17-20 November 2014; Middleburg, VA.
14. Donaldson MT, LaMonte BH, Morresey P, Smith G, Beech J. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). J Vet Intern Med. 2002;16(6):742–6.
15. Frank N, Geor R. Current best practice in clinical management of equine endocrine patients. Equine Vet Educ. 2014;26(1):6–9.
16. Copas VE, Durham AE. Circannual variation in plasma adrenocorticotropic hormone concentrations in the UK in normal horses and ponies, and those with pituitary pars intermedia dysfunction. Equine Vet J. 2012;44(4):440–3.
17. Rendle DI, Taylor E, Duz M, Parkin TD, Copas VEN, Durham AE. Effects of pergolide mesylate on plasma adrenocorticotropic hormone concentration in horses with pituitary pars intermedia dysfunction. Equine Vet J. 2013;45(S44):19.
18. Perkins GA, Lamb S, Erb HN, Schanbacher B, Nydam DV, Divers TJ. Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine Cushing's disease with cyproheptadine or pergolide. Equine Vet J. 2002;34(7):679–85.
19. Durham AE. Therapeutics for Equine Endocrine Disorders. Vet Clin North Am Equine Pract. 2017;33(1):127–39.
20. Ireland JL, McGowan CM. Epidemiology of pituitary pars intermedia dysfunction: a systematic literature review of clinical presentation, disease prevalence and risk factors. Vet J. 2018;235:22–33.
21. Durham AE, Shreeve H. Horse factors influencing the seasonal increase in plasma ACTH secretion. Paper presented at: Dorothy Russell Havemeyer Foundation Equine Endocrinology Summit; 2017; Miami, FL. https://sites.tufts.edu/equineendogroup/files/2017/01/2017-Equine-Endocrinology-Summit-D-Russell-Havemeyer-Foundation.pdf
22. Simoes J, Sales Luis JP, Tilley P. Owner compliance to an environmental management protocol for severe equine asthma syndrome. J Equine Vet Sci. 2020;87:102937.
23. Mellor DJ, Love S, Walker R, Gettinby G, Reid SW. Sentinel practice-based survey of the management and health of horses in northern Britain. Vet Rec. 2001;149(14):417–23.
24. McGowan TW, Pinchbeck G, Phillips CJ, Perkins N, Hodgson DR, McGowan CM. A survey of aged horses in Queensland, Australia. Part 1: management and preventive health care. Aust Vet J. 2010;88(11):420–7.
25. Ireland JL, Clegg PD, McGowan CM, McKane SA, Pinchbeck GL. A cross-sectional study of geriatric horses in the United Kingdom. Part 2: health care and disease. Equine Vet J. 2011;43(1):37–44.
26. Ireland JL, McGowan CM, Clegg PD, Chandler KJ, Pinchbeck GL. A survey of health care and disease in geriatric horses aged 30 years or older. Vet J. 2012;192(1):57–64.
27. MacKay C Client compliance - The key to successful veterinary practice. Presented at 30th Congress of the World Small Animal Veterinary Association; 11-14 May 2005; Mexico City, Mexico.
28. Rendle DI, Doran G, Ireland J, Edwards S. Pharmacokinetics and pharmacodynamics of pergolide mesylate after oral administration in horses with pituitary pars intermedia dysfunction. Domest Anim Endocrinol. 2019;68:135–41.

29. Rendle DI, Duz M, Beech J, Parkin T, Durham AE. Investigation of single and paired measurements of adrenocorticotropic hormone for the diagnosis of pituitary pars intermedia dysfunction in horses. J Vet Intern Med. 2015;29(1):355–61.
30. Knowles EJ, Moreton-Clack MC, Shaw S, Harris PA, Elliott J, Menzies-Gow NJ. Plasma adrenocorticotropic hormone (ACTH) concentrations in ponies measured by two different assays suggests seasonal cross-reactivity or interference. Equine Vet J. 2018;50(5):672–7.

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