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The Michigan Cushing's Project

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Clinical improvement and reversal of abnormal endocrine tests is better with pergolide treatment than with cyproheptadine treatment. In addition to being more problematic in terms of sample handling under field conditions, our data suggest that measurement of plasma adrenocorticotropin (ACTH) concentration alone may not be a reliable endocrine test for diagnosis of equine Cushing's disease. Authors' addresses: Department of Large Animal Clinical Sciences, D-202 Veterinary Medical Center, Michigan State University, East Lansing, MI 48824-1314 (Schott, Eberhart, Nachreiner, Refsal, Ewart, and Marteniuk) and American Veterinary Medical Association, 1931 North Meacham Road, Suite 100, Schaumburg, IL 60173-4360 (Coursen). © 2001 AAEP.

1. Introduction

Over the past few years, the number of horse owners wanting to maintain their equine companions through 3 and 4 decades of life has steadily increased. Simultaneously, recognition and treatment of equine Cushing's disease, attributed to adenoma/hyperplasia of the pars intermedia of the pituitary gland[1,2] has also increased. The 2 drugs most commonly used for treatment of equine Cushing's disease are cyproheptadine, a serotonin antagonist, and pergolide, a dopaminergic agonist.[3] At the 1995 Annual Meeting of the American Association of Equine Practitioners, 'low dose' pergolide therapy was advocated as the 'best' treatment for equine Cushing's disease[4]; however, to our knowledge there are no data comparing the response to treatment with these 2 drugs. Similarly, measurement of plasma adrenocorticotropin (ACTH) concentration and serum insulin concentration have been advocated, in combination with clinical signs, as accurate single sample endocrine tests for diagnosis of equine Cushing's disease.[5] However, there are no data comparing these assays with the current 'gold standards' of either a low-dose dexamethasone suppression test (DST) or a thyrotropin-releasing hormone (TRH) stimulation test (for laminitic horses).[6-8]

The Michigan Cushing's Project was initiated in 1997 as a collaborative effort between Michigan veterinarians and Michigan State University (MSU) in an attempt to answer 2 questions.

1. Are there differences in clinical and/or endocrine responses in horses with Cushing's disease that are treated with cyproheptadine, treated with pergolide, or that are not treated (3 comparison groups)?
2. How do measurements of plasma ACTH or serum insulin concentration compare with DST and TRH results in horses with Cush-

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ing's disease, and which tests are most useful for monitoring response to treatment?

2. Materials and Methods

From 1997 to 1999, 77 horses (of a total of 147 horses tested) were confirmed to have equine Cushing's disease on the basis of characteristic clinical signs and the results of either a low-dose dexamethasone suppression test[6] (DST, normal response considered suppression of plasma cortisol concentration to <30 pmol/l 17–19 hours after IM administration of 0.02 mg/kg dexamethasone) or a thyrotropin-releasing hormone stimulation test[7] (TRH, normal response considered a <30% increase in plasma cortisol concentration 15–90 minutes after IV administration of 2 μg/kg TRH). Changes in clinical examination findings (attitude, appetite, haircoat and shedding, hyperhidrosis, body condition, muscle wasting, PU/PD, and laminitis) and endocrine test results were compared at the start and after 6–12 months without treatment (NT, n = 5), or treatment with pergolide (P, 2 ug/kg PO, q 24 h, n = 20) or cyproheptadine (C, 1.2 mg/kg$^{3/4}$ PO, q 24 h, n = 7). In addition, the accuracy of plasma ACTH and serum insulin concentrations as diagnostic tests for equine Cushing's disease were compared with DST/TRH test results.

3. Results

The 77 horses initially enrolled in the study ranged in estimated age from 12–34 years (mean, 22.8 years; median, 23 years) and included a variety of breeds: Morgan (14), Quarter Horse (8), Arabian (7), Thoroughbred (4), Saddlebred (3), Appaloosa (2), Tennessee Walker (2), Pinto (2), Standardbred (1), Palamino (1), Paso Fino (1), and Holsteiner (1). Crossbreds (16) and ponies (15) were also affected. A sex predilection was not apparent as 37 (48%) were mares, 38 (49%) were geldings, and 2 (3%) were stallions.

Plasma ACTH concentration was elevated (>10 pmol/l) in 44 of 69 (64%) horses that had DST or TRH results supportive of Cushing's disease (samples were not analyzed in all horses). Serum insulin concentration was elevated (>300 pmol/l) in 54 of 76 horses that had DST or TRH results supportive of Cushing's disease (again, samples were not analyzed in all horses). Thus, for the 77 horses confirmed to have equine Cushing's disease on the basis of clinical signs and supportive DST or TRH results, nonsupportive plasma ACTH (<10 pmol/l) concentrations were measured in 25 of 69 (36%) horses, and serum insulin concentration was less than 300 pmol/l in 22 of 76 (29%) horses. Of interest, 9 of 40 horses with negative DST or TRH results had a plasma ACTH concentration greater than 10 pmol/l and 22 had a serum insulin concentration greater than 300 pmol/l. The majority of the latter hyperinsulinemic horses (53%) had laminitis as the major clinical problem and body condition was reported as follows: obese (3), fat (6), normal (6), thin (1), or emaciated (0).

Follow-up evaluation after 6–12 months of treatment revealed that clinical improvement was most apparent with P, although a few horses were also reported to improve with C. None of the NT horses were reported to have clinical improvement. DST or TRH results had returned to normal (nonsupportive of Cushing's disease) for 7 of 20, 1 of 7, and 1 of 5 of P, C, and NT horses, respectively. Chi-square analysis revealed that the proportion of horses with normal DST and TRH results after treatment was significantly greater ($p < 0.05$) for P in comparison to C or NT. Normalization of DST or TRH results was not different between C and NT. Similarly, mean plasma ACTH and serum insulin concentrations decreased significantly ($p < 0.05$) after 6–12 months of treatment with P, in contrast to a lack of significant changes with C or NT. Adverse treatment effects were not reported with C, but several P-treated horses were reported to have a decrease in appetite during the first week of treatment. Reduction of the dose for a few days seemed helpful in resolving the partial anorexia in these horses.

4. Discussion

This field study of horses with naturally occurring equine Cushing's disease provides a number of novel observations about the treatment and progression of an important problem of older horses. First, the results clearly demonstrate that treatment with pergolide produced clinical and laboratory responses that were superior to treatment with cyproheptadine. In fact, treatment with cyproheptadine was found to be of little benefit when responses were compared with those observed in horses receiving no treatment. Second, measurement of plasma ACTH concentration was found to produce both false positive and false negative results, when compared with DST or TRH results for diagnosis of a pituitary adenoma. Third, identification of a group of horses with abnormal fat deposition and laminitis, without hirsutism, which had elevated serum insulin concentrations and normal DST or TRH results, provides further support that a recently described peripheral Cushing's disease syndrome[9] may be a differential diagnosis for horses with a suspected pituitary adenoma. This latter observation is important because horses with a peripheral Cushing's disease syndrome would not be expected to improve with treatment with pergolide.

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