Pulmonary function and adrenal gland suppression with incremental doses of aerosolized beclomethasone dipropionate in horses with recurrent airway obstruction

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Objective—To evaluate clinical response, pulmonary function, and adrenal gland response to incremental doses of beclomethasone dipropionate in horses with recurrent airway obstruction.

Design—Crossover trial.

Animals—8 horses with recurrent airway obstruction.

Procedure—Horses randomly assigned to 4 groups were treated twice daily via aerosol administration of placebo or 500, 1,000, or 1,500 µg of beclomethasone dipropionate in a crossover design with a 10-day minimum washout period. Subjective assessment of airway obstruction, serum cortisol concentration, and maximum change in pleural pressure during tidal breathing (ΔPPlmax) were determined daily prior to morning drug administration, and ΔPPlmax was reevaluated 15 minutes after morning drug administration. Pulmonary resistance and dynamic compliance were determined at baseline and approximately 12 hours after the final treatment.

Results—An immediate treatment effect was not identified. Within 24 hours, ΔPPlmax and airway obstruction were lower in horses receiving beclomethasone. Onset and magnitude of response was similar among the 3 beclomethasone dose regimens. Pulmonary resistance was improved only after administration of all 3 doses of beclomethasone, whereas dynamic compliance was improved after administration of 1,000 µg and 1,500 µg of beclomethasone. Reduction in serum cortisol concentration occurred with all 3 beclomethasone dose regimens; however, the magnitude of adrenal gland suppression was greater in horses receiving 1,000 or 1,500 µg of beclomethasone.

Conclusions and Clinical Relevance—Low-dose (500 µg) beclomethasone administration caused similar improvement in pulmonary function, compared with high-dose beclomethasone (1,000 and 1,500 µg), with the exception of dynamic compliance, and caused less suppression of endogenous cortisol production. (J Am Vet Med Assoc 2000;217:359–364)

Beclomethasone dipropionate is a surface-active corticosteroid preparation that is widely prescribed for anti-inflammatory treatment for human asthmatic patients.1 Aerosolized beclomethasone reduces clinical signs of airway obstruction, improves measurements of pulmonary function, and constitutes first-line treatment for patients with mild to moderate asthma.2 Daily administration of aerosolized corticosteroids as maintenance treatment reduces the frequency of asthmatic episodes and usually eliminates the need for treatment with bronchodilators.1 At therapeutic doses (800 to 1,500 µg/d), aerosolized beclomethasone does not induce clinically relevant adrenal gland suppression and is considered safer than corticosteroid administration via routes that have greater systemic effects.3

Administration of aerosolized beclomethasone improves measures of pulmonary function and reduces pulmonary inflammation in horses with recurrent airway obstruction (heaves).5,7 Improvement in clinical signs of airway obstruction develops within 3 days of initiation of treatment. However, horses are more sensitive to the adrenosuppressive effects of aerosolized beclomethasone than humans. The threshold for adrenal suppression with short-term (5-day) administration is approximately 500 µg of beclomethasone administered twice daily.6 Adrenal gland suppression develops in horses with heaves and horses with normal respiratory function with higher dose regimens. Administration of beclomethasone in excess of 1,000 µg (q 12 h) induces 35% reduction in morning serum cortisol concentration within 24 hours and 80% reduction after 5 days.6,8 Serum cortisol concentrations recover within 2 days of discontinuation of treatment, and adrenal gland responsiveness to exogenous adrenocorticotrophic hormone is preserved.9

The efficacy of beclomethasone at minimally adrenosuppressive doses has not been established in horses with recurrent airway obstruction. The objectives of the study reported here were to evaluate the clinical response, pulmonary function, and adrenal gland response to incremental doses of beclomethasone dipropionate in horses with recurrent airway obstruction.

Materials and Methods

Eight horses (5 geldings, 3 mares; 13 to 28 years of age) with inductive and reversible recurrent airway obstruction were used in this investigation. The horses were owned by Kansas State University and were maintained in remission at pasture between experimental studies. Reversible airway obstruction was confirmed in affected horses by positive response to atropine challenge and remission of clinical signs during pasture housing. Episodes of airway obstruction were induced by housing horses in a barn and placing moldy hay and straw in their environment.10 A maximal change in

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pleural pressure during tidal breathing ($\Delta P_{\text{pl}}_{\text{max}}$) of 15 cm H$_2$O was required for inclusion in the investigation. Horses remained in the confined moldy environment for a 7-day treatment period and for final evaluation on day 8. This investigation was approved by the Animal Care and Use Committee of Kansas State University. Horses were removed from the study if $\Delta P_{\text{pl}}_{\text{max}}$ exceeded 60 cm H$_2$O or horses failed to eat a grain ration.

Horses were randomly assigned to 4 treatment groups in a crossover design with a 10-day minimum wash-out period. Treatment groups consisted of 3 doses of aerosolized beclomethasone dipropionate$^a$ (500, 1,000, and 1,500 $\mu$g) and aerosolized placebo (15 actuations propellant) administered every 12 hours. Beclomethasone dipropionate and placebo propellant were administered into the left nostril with an equine-adapted hand-held metered-dose delivery device.$^{1,10}$ The incremental doses of beclomethasone corresponded to 5, 10, and 15 actuations of the metered-dose delivery device.

Subjective clinical assessment of respiratory effort and respiratory frequency were determined daily throughout the 8-day evaluation period by a single investigator (BRR) blinded to the treatment groups. The subjective rating of airway obstruction (RAO) scoring system to evaluate respiratory effort was adopted from Robinson et al.$^{1}$ Abdominal expiratory effort was evaluated on a scale of 1 to 4, as follows: 1 = clinically normal, no signs; 2 = slight abdominal component; 3 = moderate abdominal component; 4 = severe, continuous flaring during each breath. Minimum total RAO score was 2, and the maximum RAO score was 8.

The $\Delta P_{\text{pl}}_{\text{max}}$ was determined each morning of the 8-day investigational period prior to drug administration; baseline evaluation was obtained on day 1, and the final evaluation was obtained on day 8 (approx 12 hours after the final treatment). In addition, $\Delta P_{\text{pl}}_{\text{max}}$ was determined 15 minutes after morning drug administration each day to investigate an immediate drug effect. Pulmonary resistance ($R_L$) and dynamic compliance ($C_{\text{dyn}}$) were determined on day 1 prior to morning drug administration and on day 8 (approx 12 hours after the final treatment). Serum cortisol concentration was determined for 8 consecutive days for each horse during each treatment regimen.

Pleural pressure was obtained by use of a latex esophageal balloon (length, 10 cm; diameter, 3.5 cm; thickness, 0.6 mm)$^7$ sealed over a tellon catheter (internal diameter, 3 mm; outer diameter, 4.4 mm; length, 240 cm)$^{11,12}$ The balloon and catheter were passed through the nares into the distal portion of the esophagus. The catheter was connected to a differential pressure transducer$^8$ and the signal was amplified$^9$ and recorded with a lung-function computer.$^{15}$ The pressure transducer was calibrated to 80 cm H$_2$O with a water manometer. The position of the catheter was adjusted to obtain the $\Delta P_{\text{pl}}_{\text{max}}$.

Flow rate was obtained by use of a pneumotachograph (No. 6 Fleisch)$^9$ fitted in a sealed face mask placed over the horse’s muzzle. The pneumotachograph was attached to a differential pressure transducer$^8$ and connected to the lung-function computer. Tidal volume was determined by electronic integration of the flow signal tracing. The system was calibrated by forcing known volumes and flow rates, determined by use of a spirometer, through the pneumotachograph. Regression analysis was performed on a calibration curve, and a regression equation was produced to calculate flow values. Flow, tidal volume, and $\Delta P_{\text{pl}}_{\text{max}}$ were processed by the lung-function computer and a physiograph trace generated for breath-by-breath values. These tracings were used for breath-by-breath calculation of $R_L$ and $C_{\text{dyn}}$.$^{19}$ At each data collection period, mean values of 20 to 30 consecutive breaths were determined for each measure of pulmonary function.$^{5}$

Serum samples for cortisol determination were separated from blood samples obtained between 7:00AM and 8:00AM prior to initiation of treatment on day 1 and prior to morning drug administration on days 2 to 8. Serum cortisol concentrations were determined by use of chemiluminescent enzyme immunoassay and an automated analyzer system.$^{6}$ The limits of detection of the assay were 2.8 to 1,380 nmol/L, and intra- and interassay precision ranged from 90 to 94%. Serum samples were stored for 2 weeks (maximum) at –20°C until assayed.

Statistical analyses—Comparisons of results of pulmonary function testing, serum cortisol concentration, and respiratory scoring were made by use of a 2-way ANOVA for repeated measures. When significant ($P < 0.05$) differences were determined, post hoc comparisons were made by use of a Newman-Keuls test.

**Results**

Maximal change in pleural pressure—Differences in $\Delta P_{\text{pl}}_{\text{max}}$ were not detected among treatment groups at baseline (day 1) or in placebo-treated horses throughout the 8-day evaluation period (Fig 1). Throughout the treatment period (day 2 to day 8), $\Delta P_{\text{pl}}_{\text{max}}$ was significantly lower ($P < 0.05$) in horses receiving 500 $\mu$g and 1,500 $\mu$g of beclomethasone, compared with placebo-treated horses. Differences were not detected between 500-$\mu$g and 1,500-$\mu$g treatment groups throughout the treatment period. In horses receiving 1,000 $\mu$g of beclomethasone, a significant treatment effect was detected on days 4, 6, 7, and 8, compared with placebo-treated horses.

Mean percent reduction in $\Delta P_{\text{pl}}_{\text{max}}$ 15 minutes after morning drug administration was similar among the 4 treatment groups: 10.3 ± 2.1% in placebo-treated horses, 1.8 ± 4.1% in horses receiving 500 $\mu$g of beclomethasone, 12.0 ± 2.6% in horses receiving 1,000 $\mu$g of beclomethasone, and 12.0 ± 2.6% in horses receiving 1,000 $\mu$g of beclomethasone.$^{12}$
µg of beclomethasone, and 9.0 ± 2.5% in horses receiving 1,500 µg of beclomethasone.

Rating of airway obstruction—Differences were not detected in subjective RAO scores among treatment groups at baseline (day 1) or in placebo-treated horses throughout the 8-day evaluation period (Fig 2). Subjective clinical scores were significantly reduced in all 3 treatment groups from day 2 through day 8, compared with placebo-treated horses. The magnitude of reduction in clinical scores was similar among the 3 treatment groups.

Serum cortisol concentration—Differences in serum cortisol concentration among treatment groups at baseline (day 1) were not detected. A gradual decline in serum cortisol concentration was detected in placebo-treated horses throughout the 8-day investigation period; this was a significant (P < 0.05) decrease from baseline values on days 7 and 8 (Fig 3). Serum cortisol concentrations of horses receiving 500 µg of beclomethasone were significantly (P < 0.05) lower than those of placebo-treated horses on days 3, 4, 5, and 6. Serum cortisol concentrations of horses receiving 1,000 and 1,500 µg of beclomethasone were significantly (P < 0.01) lower than those of placebo-treated horses throughout the treatment period (days 2 through 8). On days 7 and 8, serum cortisol concentrations were significantly lower in horses receiving 1,000 and 1,500 µg of beclomethasone, compared with horses receiving 500 µg.

Pulmonary resistance—One horse did not tolerate the sealed facemask on day 1 or day 8 during the 1,500-µg treatment period; therefore, RL and Cdyn values were determined for 7 horses in the 1,500-µg treatment group. Differences in RL among treatment groups were not detected at baseline (day 1). A 17.6% reduction (P = 0.17) in RL after the 7 day treatment period was detected in placebo-treated horses (Fig 4). A significant (P < 0.05) reduction in RL was detected in beclomethasone-treated horses, compared with placebo-treated horses; the magnitude of change was similar among the 3 doses of beclomethasone.

Dynamic compliance—Differences in dynamic compliance among treatment groups were not detected at baseline (day 1). A 21% mean increase (P = 0.26) in Cdyn after the 7-day treatment period was detected in placebo-treated horses (Fig 5). A significant (P < 0.05) increase in Cdyn was detected in horses receiving 1,000 µg of beclomethasone and 1,500 µg of beclomethasone, compared with placebo-treated horses. Mean increase in Cdyn in horses receiving 500 µg of beclomethasone was not different from the change in placebo-treated horses (P = 0.109); the range of percentage change in Cdyn was –27 to 660% in this treatment group. In addition, Cdyn values obtained on day 8 were significantly higher than baseline compliance values in horses receiving 500 µg of beclomethasone.

One horse was withdrawn from a 7-day treatment period (placebo) on day 3 because of colonic impaction; the entire 7-day placebo treatment period was repeated after a 4-week rest period. One horse was withdrawn from a 7-day treatment period (500 µg of beclomethasone, q 12 h) on day 5 because of fever and
tic doses (800 to 1,500 µg) increasingly recognized to have more rapid onset of response in human asthmatic patients, inhaled corticosteroids are commonly associated with adverse effects in human asthmatic patients and marginally improve treatment efficacy. In one study, the increasing tendency to use higher doses of inhaled corticosteroids on the basis of the assumption that there are clear dose-response benefits is misguided and not supported by reliable published information. The therapeutic advantage is minimal and considered clinically unimportant by most investigators. Endogenous cortisol production was suppressed in horses receiving all 3 doses of inhaled beclomethasone. The magnitude of adrenal gland suppression was more severe in horses receiving 1,000 and 1,500 µg, compared with cortisol concentrations in horses receiving 500 µg. Differences were not detected between mean serum cortisol concentrations of placebo- and 500-µg treatment groups on the final 2 days of the investigation, however, mean values were approximately 35% lower in the 500-µg treatment group. Horses are more sensitive than humans to the adrenocorticotropic effects of beclomethasone.

In human asthmatic patients, morning serum cortisol concentration is minimally altered by high-dose beclomethasone, and more sophisticated tests are required to detect suppression of the hypothalamic-pituitary-adrenal (HPA) axis, including 24-hour urine-free cortisol excretion and adrenocorticotropic hormone stimulation. Disruption of the HPA axis is the most sensitive indicator of systemic absorption of beclomethasone. In this investigation, administration of 1,500 µg of beclomethasone (q 12 h, for 7 days) reduced serum cortisol concentrations by 93%.

Figure 5—Dynamic compliance (mean ± SD) in horses with recurrent airway obstruction after a 7-day aerosol treatment regimen with placebo or beclomethasone. *Significant (P < 0.05) difference in percentage change from baseline, compared with placebo-treated horses.

Discussion

Administration of aerosolized beclomethasone dipropionate improved measures of pulmonary function and clinical signs of airway obstruction in this population of horses with recurrent airway obstruction. Therapeutic benefit of beclomethasone administration was observed 24 hours after initiation of treatment with all 3 dosage regimens, and the magnitude of improvement was similar among the 3 treatment groups. Clinical signs of airway obstruction and pulmonary function values continued to gradually improve throughout the 7-day treatment period.

No immediate (15-minute) treatment effect was identified, indicating beclomethasone should not be administered as a rescue drug for horses with severe signs of airway obstruction. Treatment with a bronchodilator is a more appropriate rescue treatment for horses with dyspnea, providing immediate relief of airway obstruction. In addition, treatment with a bronchodilator before administration of an aerosolized surface-active corticosteroid preparation may improve pulmonary distribution of the corticosteroid.

Response to treatment was detected earlier in this study than in previous investigations of aerosolized beclomethasone in horses with heaves. Twenty-four hours after initiation of treatment, ∆Pplmax improved by 25 to 50% of baseline values, and scores for airway obstruction were significantly lower than those of placebo-treated horses. To the authors’ knowledge, daily pulmonary function testing to evaluate efficacy of beclomethasone has not been reported; other studies evaluated effects every 3 to 7 days. In one study, duration of the induction period was prolonged (1 month); therefore, response to treatment may have been delayed by the chronicity of inflammation. In human asthmatic patients, inhaled corticosteroids are increasingly recognized to have more rapid onset of action than previously detected. At standard therapeutic doses (800 to 1,500 µg/d), response to beclomethasone administration typically is observed 72 to 96 hours after initiation of treatment; however, improvement in airway hyperreactivity and results of pulmonary function testing has been detected within 32 hours when higher dose regimens (2,000 µg, q 12 h) are used. In the study reported here, there was no advantage in onset of action or magnitude of response in the first 72 hours with higher (1,000 and 1,500 µg) dose regimens. In fact, the 1,000-µg treatment group did not respond as well as the 500-µg treatment group during the first 35% lower in the 500-µg treatment group. Horses are more sensitive than humans to the adrenocorticotropic effects of beclomethasone. In human asthmatic patients, morning serum cortisol concentration is minimally altered by high-dose beclomethasone, and more sophisticated tests are required to detect suppression of the hypothalamic-pituitary-adrenal (HPA) axis, including 24-hour urine-free cortisol excretion and adrenocorticotropic hormone stimulation. Disruption of the HPA axis is the most sensitive indicator of systemic absorption of beclomethasone. In this investigation, administration of 1,500 µg of beclomethasone (q 12 h, for 7 days) reduced serum cortisol concentrations by 93%.
Clinical consequences of adrenal gland suppression were not detected in this treatment group during the investigation; however, administration of an exogenous corticosteroid that induces this magnitude of adrenal gland suppression for a prolonged treatment period does have the potential to cause clinical signs of iatrogenic hypothalamic-pituitary-adrenal (HPA) axis suppression. The clinical impact of mild adrenal gland suppression associated with administration of low-dose beclomethasone (300 μg, q 12 h) for a prolonged treatment period in horses is uncertain.

The magnitude and onset of adrenal gland suppression in this population of horses with heaves is similar to that reported for horses with normal respiratory function. Pulmonary inflammation and impaired pulmonary drug distribution does not appear to alter systemic absorption of beclomethasone in horses with recurrent airway obstruction. This response has been reported in horses with heaves, and we suspect that the decline results from adaptation to a chronic environment and experimental manipulation during the week-long investigation. The formulation of beclomethasone dipropionate used in our study contains the chlorofluorocarbon (CFC)-free propellant hydrofluoroalkane-134a (HFA). This formulation produces a solution that provides a greater total mass of fine drug particles than CFC propellants, resulting in improved delivery of beclomethasone to the large and small airways in humans. Equivalent improvements in asthma control are accomplished with a daily dose of HFA-beclomethasone that is half the required dose of CFC-beclomethasone. Greater systemic availability of HFA-beclomethasone does not cause greater adrenal gland suppression; the adrenal gland effects and acute local tolerability are comparable to that of the CFC formulation at the same dose. Equivalent efficacy at a lower dose and equivalent safety at the same dose indicates a more favorable risk-benefit ratio for HFA-beclomethasone. Comparison studies of HFA- and CFC-beclomethasone have not been performed on horses. Enhanced drug delivery and efficacy of HFA-beclomethasone may explain, in part, why treatment with low doses of beclomethasone, compared with standard therapeutic doses in human asthmatics, is effective in horses with heaves.

In the study reported here, horses remained in an allergen-challenged environment during the treatment period, concurrent medications were not administered, the induction period was short (7 days), and severity of disease was substantial. In clinical practice, duration and severity of disease will vary among affected horses, and recommendations for reduction of allergen exposure and concurrent treatment with bronchodilators are common. Results of the study reported here provide information regarding safety and efficacy of aerosolized beclomethasone for treatment of recurrent airway obstruction, under the conditions described, in horses with clinical signs of airway obstruction at rest. The relative impact of individual factors (chronicity or severity of disease, allergen exposure, concurrent treatment with bronchodilators) on response to treatment is unknown. Clinicians are encouraged to administer the lowest effective dose of beclomethasone for treatment of individual patients with recurrent airway obstruction.

References


