

Nebulized dexamethasone sodium phosphate in the treatment of horses with severe asthma

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Abstract

Background: A study reported low systemic availability of injectable dexamethasone nebulized to healthy horses using the Flexineb mask. When used in horses with severe asthma and a different nebulizer, lack of efficacy and cortisol suppression were observed.

Hypothesis: Nebulized dexamethasone is as effective as PO administration for the treatment of severe asthma in horses.

Animals: Twelve horses with severe asthma from a research herd.

Methods: Randomized clinical trial. Horses were divided into 2 groups and received 5 mg of dexamethasone sodium phosphate by nebulization using a Flexineb mask (NE, $n = 6$) or PO (OR, $n = 6$) q24h for 7 days. Lung function and serum cortisol concentrations were evaluated at baseline, after 4 days of treatment (D4) and 1 day after the last treatment (D8). Data were analyzed using linear mixed models with Benjamini-Hochberg adjustments.

Results: Lung resistance significantly improved at D4 (mean decrease \pm SD, -1.5 ± 0.45 cm H₂O/L/s; 95% confidence interval [CI], -2 ; -0.6) and D8 (-1.4 ± 0.45 cm H₂O/L/s; 95% CI, -2.4 ; -0.5) compared to baseline in the OR group only ($P = .004$ and $.01$, respectively). Serum cortisol concentration was significantly decreased at D4 and D8 for both groups (maximum decrease, -1.2 ± 0.3 μ g/dL; 95% CI, -1.9 ; -0.6 at D4 for NE group and -2.2 ± 0.3 μ g/dL; 95% CI, -2.8 ; -1.6 at D8 for OR group; $P < .001$).

Conclusions and Clinical Importance: Oral, but not nebulized dexamethasone is an effective therapy for horses with severe asthma and both treatment modalities inhibit the hypothalamic-pituitary-adrenal axis.

KEYWORDS

corticosteroids, cortisol, heaves, hypothalamic-pituitary-adrenal axis suppression, inhalation, lung, recurrent airway obstruction

Abbreviations: CI, confidence interval; E_L , lung elastance; HPA axis, hypothalamic-pituitary-adrenal axis; NE, nebulized; OR, oral; P_L , transpulmonary pressure; R_L , lung resistance.

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1 | INTRODUCTION

Severe asthma in horses is a debilitating and incurable condition affecting approximately 14% of adult horses in temperate countries such as Great Britain.¹ This inflammatory condition of the lower airways is caused by exposure to antigens present in the environment, especially those found in hay and bedding.² Clinical signs in horses during exacerbation of severe asthma are exercise intolerance, cough and increased respiratory efforts at rest.³ The cornerstone treatment of severe asthma in horses is antigen avoidance, but adequate control of the environment is not always possible and medical treatment may be needed.⁴⁻⁶ Corticosteroids are the most effective drugs to improve lung function in horses with severe asthma.^{5,7} However, when prolonged treatment is required, corticosteroids can lead to adverse effects,⁶ such as hypothalamic-pituitary-adrenal (HPA) axis suppression,^{8,9} immunosuppression and laminitis. Inhaled corticosteroids are effective and may be associated with fewer adverse effects than systemically-administered corticosteroids.^{3,10}

Previous studies have demonstrated the efficacy of nebulized dexamethasone to control asthma in humans.^{11,12} Inhaled dexamethasone recently was shown to result in low plasma concentrations in healthy horses without suppressing the HPA axis.¹³ However, when evaluated for the treatment of horses with severe asthma, nebulized dexamethasone failed to improve lung function parameters after 7 days of treatment.¹⁴ Furthermore, it was associated with a decrease in basal serum cortisol concentration, suggesting potentially adverse systemic effects. The main differences between these 2 studies were the horses' clinical status and the nebulizers used to deliver dexamethasone. Whether the delivery and absorption of drugs differed between the 2 devices or were modified because of changes in the airways and breathing patterns caused by asthma was not determined.

We hypothesized that the lack of efficacy and systemic absorption observed in horses with asthma could be a consequence of the nebulizer used. Our objective therefore was to determine whether a better clinical outcome would be observed with nebulized dexamethasone using the device previously studied in healthy horses.

2 | MATERIALS AND METHODS

2.1 | Animals and housing

Twelve mature horses (7 mares and 5 geldings) from a research herd were included in the study. They were mixed breeds, aged 11 to 27 years (mean \pm SD, 16 \pm 6 years) and weighed 442 to 612 kg (mean \pm SD, 509 \pm 53 kg). The horses previously had been diagnosed with severe asthma based on history, lung function measurements (difference in transpulmonary pressure >15 cm of H₂O) and bronchoalveolar lavage cytology results (>20% neutrophils). All horses were in disease remission with normal physical examination findings because of having been kept at pasture before the study.

Horses were stabled together in individual box stalls for 16 to 20 days before baseline lung function measurements. They were fed twice a day (between 8:30 and 9:00 AM and at 5:00 PM) with hay of various quality and turned out 2-6 hours per day. Hay quality and time spent outside were adapted for each horse to induce and maintain appropriate clinical signs. Conditions remained unchanged for at least 1 week before study initiation and during the entire study period. Horses previously had been accustomed to collection of lung function measurements and the nebulization procedure. The study was performed at the Faculty of Veterinary Medicine of the University of Montreal. All procedures were approved by the Animal Care Committee of the Faculty (Protocol # 18-Rech-1935).

2.2 | Study design

To obtain groups of comparable severity, lung function was measured at baseline, and then horses were ranked according to lung resistance (R_L) and separated into 2 groups (A and B): the horse with the highest R_L was allocated to group A, the horse with the second highest R_L to group B and so on. Groups then were randomly assigned to treatment by tossing a coin. One group of horses received dexamethasone by nebulization (NE group), and the other received dexamethasone PO (OR group) for 7 days. Lung function was measured on days 4 and 8. On day 8, pulmonary function tests were repeated 10 minutes after administration of a bronchodilator (N-butylscopolammonium bromide; Buscopan, Boehringer Ingelheim Ltd, Burlington, ON, Canada; 0.3 mg/kg IV). The bronchodilator was used to assess the reversibility of residual bronchospasm at the end of the treatment period. Serum cortisol concentrations were determined on days 0, 4, and 8 (24 hours after the last dose of dexamethasone).

2.3 | Medication

Horses were given dexamethasone sodium phosphate (Dexamethasone 5, Vetoquinol N.-A. Inc, Lavaltrie, QC, Canada; 5 mg PO q24h in the morning) between 7:00 and 8:00 AM, before feeding, for 7 days. Dexamethasone was diluted 1:1 with sterile saline for both groups and administered by nebulization using a commercial mask (Flexineb E2, Nortev Ltd, Claregalway, Galway, Ireland) or PO using a 5 mL syringe. The commercial device was used according to the manufacturer's instructions and washed with water and soap between each horse. The nebulizer took approximately 2.5 minutes to administer the dose of dexamethasone, the mask was kept on the horse's face for 3 minutes to standardize administration time.

2.4 | Clinical follow-up

Respiratory clinical scores (scale 1 to 4 for nasal flaring and for abdominal movement)¹⁵ were determined every morning by the same

investigator before treatments. The investigator was aware of the horse's treatment group.

2.5 | Lung function

Standard lung function measurement was performed on standing unsedated horses, except for 1 horse that required xylazine (Rompun, Bayer Inc, Mississauga, ON, Canada; 180 mg IV) for naso-esophageal intubation. An esophageal balloon was placed in the distal third of the esophagus to estimate transpulmonary pressure (P_L). Airflow was determined using a heated pneumotachograph placed on a nasal mask. Software (Flexiware 7.6, SCIREQ, Montreal, Quebec, Canada) was used to calculate lung resistance (R_L) and lung elastance (E_L) by applying the multiple regression equation used for the single compartment model of the lung [$P_L = (E_L \times V) + (R_L \times \dot{V}) + K$], with V the volume, \dot{V} the airflow, and K the transpulmonary end expiratory pressure) to the data measured. Coefficients of determination for the fit of the equation to the measures were calculated for each breath, and all valid breaths were used for statistical analysis, with a minimum of 10.

2.6 | Serum cortisol measurements

Blood was collected between 7:00 and 8:00 AM at baseline, on day 4 (before treatment) and on day 8. Blood was centrifuged at 2000 rpm for 10 minutes and serum was collected and stored at -80°C within 90 minutes after collection. Serum cortisol concentration was measured by chemiluminescence (Immulite, Siemens, Erlangen, Germany). The detection limit was $0.36 \mu\text{g/dL}$ (10 nmol/L). Results below this limit were assigned a concentration of $0.36 \mu\text{g/dL}$ for statistical analysis.

2.7 | Statistical analysis

Values for P_L , R_L , and E_L were analyzed using linear mixed models with horse identification nested within group (NE or OR) as random effect and the following fixed effects: group, time, and the interaction between the 2. The same approach was used for cortisol concentrations. The effect of the bronchodilator on lung parameters was evaluated using a linear mixed model with horse identification nested within group as random effect and the following fixed effects: group, time (before and after administration) and the interaction between the 2. After each linear mixed model, we performed a priori contrasts to compare baseline results in each group with results at each time and to compare the 2 groups at each time. For these contrasts, the alpha value (initially 5%) was adjusted downward using the Benjamini-Hochberg procedure. Statistical analyses were carried out using SAS v.9.3 (Cary, North Carolina). Graphics were generated using Prism 8 (GraphPad Software Inc, La Jolla, California).

3 | RESULTS

3.1 | Pulmonary function tests

All horses had exacerbated asthma at baseline ($P_L > 15 \text{ cm H}_2\text{O}$, $R_L > 1 \text{ cm H}_2\text{O/L/s}$, and $E_L > 1 \text{ cm H}_2\text{O/L}$). No differences were found between the OR and the NE group at baseline for P_L , R_L , and E_L . There was an effect of time for P_L ($P = .02$), R_L ($P = .003$), and E_L ($P = .01$) but no effect of treatment group or interaction between time and group. In the OR group only, a mild but significant decrease of R_L was identified at D4 (mean \pm SD, $1.8 \pm 0.8 \text{ cm H}_2\text{O/L/s}$; $P = .004$) and D8 (mean \pm SD, $1.9 \pm 1.1 \text{ cm H}_2\text{O/L/s}$; $P = .01$) when compared to baseline results (mean \pm SD, $3.3 \pm 0.9 \text{ cm H}_2\text{O/L/s}$; Figure 1B). The E_L was decreased in the OR group at D4 ($1.9 \pm 1.3 \text{ cm H}_2\text{O/L}$; $P = .01$; not significant after adjustment of the alpha threshold) and D8 ($3.5 \pm 3.5 \text{ cm H}_2\text{O/L}$; $P = .06$) when compared to baseline ($6.9 \pm 4.4 \text{ cm H}_2\text{O/L}$; Figure 1C). The P_L decreased in the OR group at D4 ($25 \pm 10.6 \text{ cm H}_2\text{O}$; $P = .01$) and D8 ($32 \pm 25.4 \text{ cm H}_2\text{O}$; $P = .05$) when compared to baseline ($54 \pm 23.6 \text{ cm H}_2\text{O}$), but results were not significant after adjustment (Figure 1A). In the nebulized group, E_L and P_L did not decrease (Figure 1A,C).

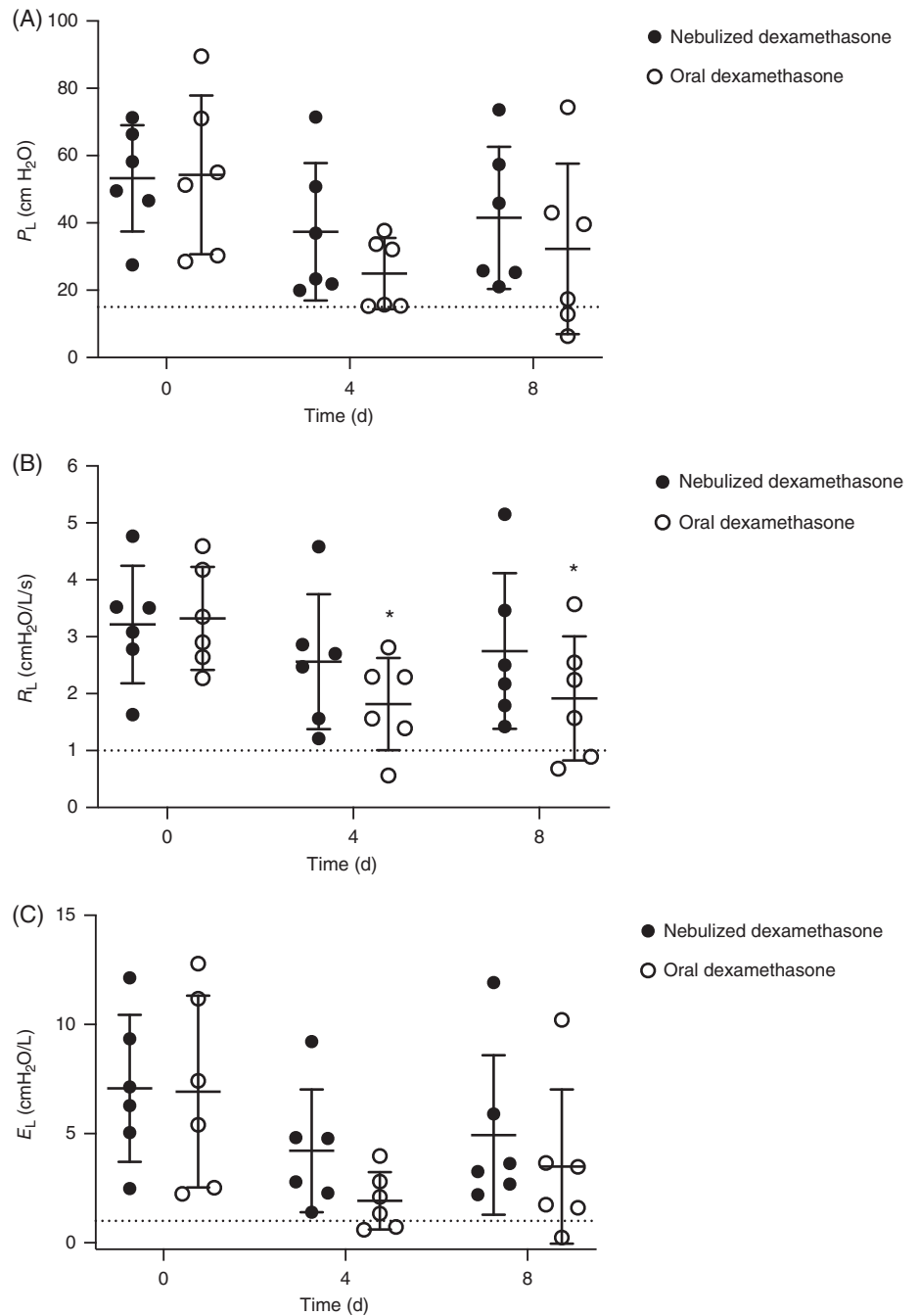
3.2 | Residual bronchospasm

Twenty-four hours after the last treatment (D8), administration of a bronchodilator induced a decrease of P_L and R_L in the NE group from 42 ± 21 to $19 \pm 7.7 \text{ cm H}_2\text{O}$ ($P = .01$) and 2.7 ± 1.4 to $1.5 \pm .5 \text{ cm H}_2\text{O/L/s}$ ($P = .01$), respectively, but not in the OR group ($P = .03$ and $P = .04$, respectively, but not significant after adjustment; Figure 2A, B). The E_L decreased after bronchodilator administration in both groups ($P = .02$ in NE group, not significant after adjustment, and $P = .1$ in OR group, Figure 2C).

3.3 | Serum cortisol concentrations

At baseline, serum cortisol concentration was not different between groups ($3.1 \pm 1 \mu\text{g/dL}$ and $3.2 \pm 1.1 \mu\text{g/dL}$ in the OR and NE groups, respectively; $P = .9$; Figure 3). Basal serum cortisol concentration decreased in all horses with an effect of time ($P < .001$) but no effect of treatment ($P = .15$). An interaction between time and treatment group was found ($P = .05$). The decrease in basal serum cortisol concentration was significant in both groups at D4 ($1.2 \pm 1.1 \mu\text{g/dL}$; $P < .001$ and $1.9 \pm 0.6 \mu\text{g/dL}$; $P = .001$ in OR and NE groups, respectively) and D8 ($0.9 \pm 0.7 \mu\text{g/dL}$; $P < .001$ and $2.1 \pm 0.6 \mu\text{g/dL}$, $P = .003$ in OR and NE groups, respectively) when compared to baseline. No difference was found in serum cortisol concentration between groups at each time but serum cortisol concentration was lower at D8 ($P = .02$, not significant after adjustment) in the OR group when compared to the NE group. At D8, half of the horses in the OR group (3/6), but none in the NE group, had serum cortisol concentrations below the detection limit ($0.36 \mu\text{g/dL}$).

FIGURE 1 Transpulmonary pressure (P_L ; A), lung resistance (R_L ; B) and lung elastance (E_L ; C) (the horizontal lines represent the mean \pm SD) at baseline, on treatment day 4, and 1 day after the last treatment (day 8) in horses with severe asthma treated with nebulized (black circles; $n = 6$) or PO (white circles; $n = 6$) dexamethasone (5 mg q24h). The dotted line represents values expected from healthy horses. * represents significant difference from baseline



4 | DISCUSSION

In agreement with the results of a previous study,¹⁴ nebulized dexamethasone failed to significantly improve the lung function of horses with severe asthma. Furthermore, it suppressed serum cortisol concentrations, suggesting the potential for adverse systemic effects with chronic use. These results contrast with those obtained in healthy horses.¹³ It had been postulated that the differences in response to inhaled dexamethasone between healthy and horses with asthma were caused by the use of different nebulizers.¹⁴ Particle size and density generated by inhalation devices are characteristics of the device used and also vary depending on the solution administered,

affecting distribution of drugs within the airways¹⁶ and resulting in variable local beneficial effects and systemic absorption. However, our study ruled out this hypothesis because the nebulizer was similar to that used in healthy horses.¹³ Therefore, the most probable explanation for the difference observed between healthy horses and horses with asthma is an alteration in drug distribution and absorption in diseased animals, as described in humans.¹⁷⁻¹⁹

Adequate drug deposition in the distal airways is impeded by modifications in breathing patterns, cough, bronchoconstriction, and airway secretions such as mucus,¹⁰ which often are present in asthmatic horses. In diseased humans, more central drug deposition occurs compared to healthy patients.^{17,20} Because mucociliary clearance is

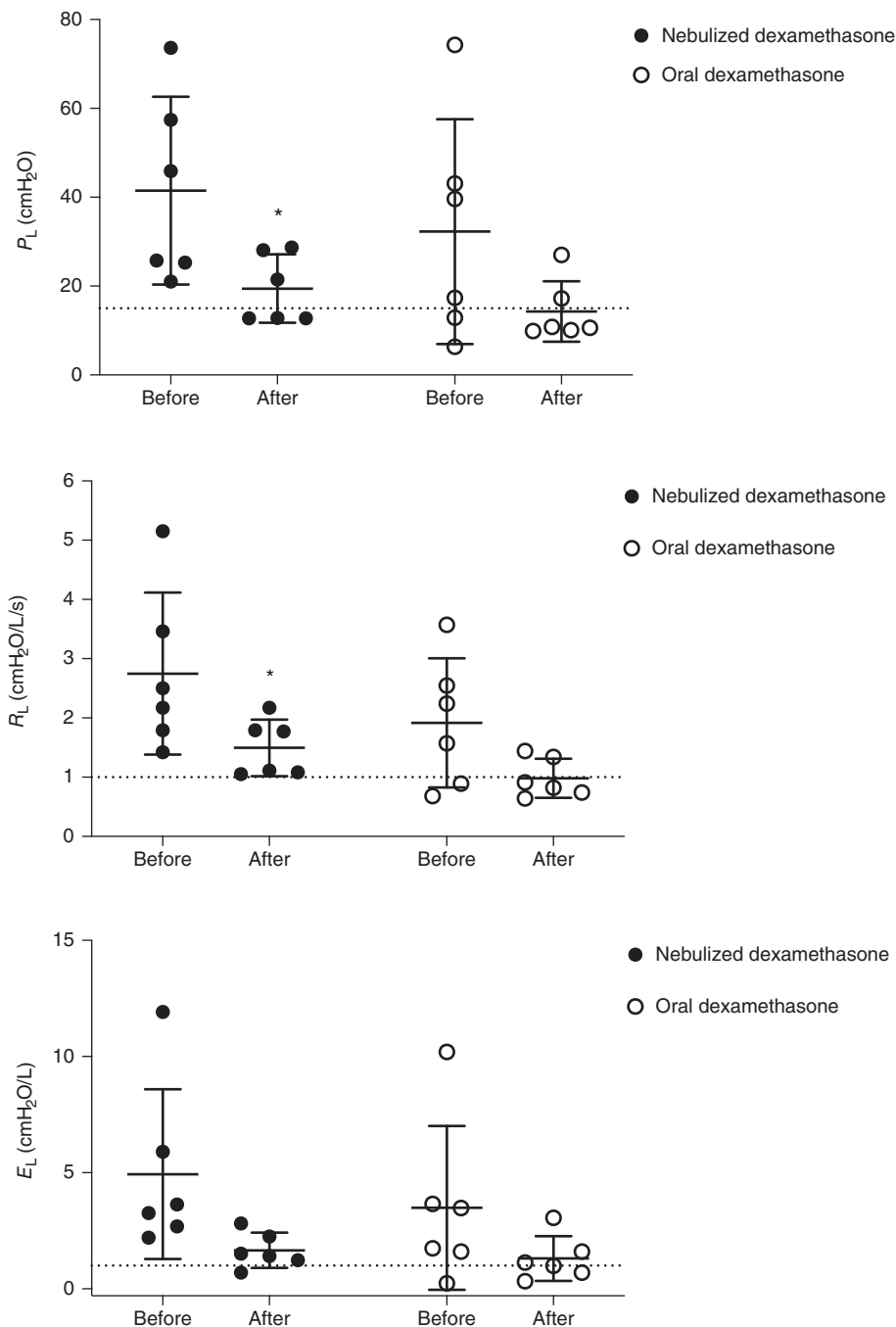


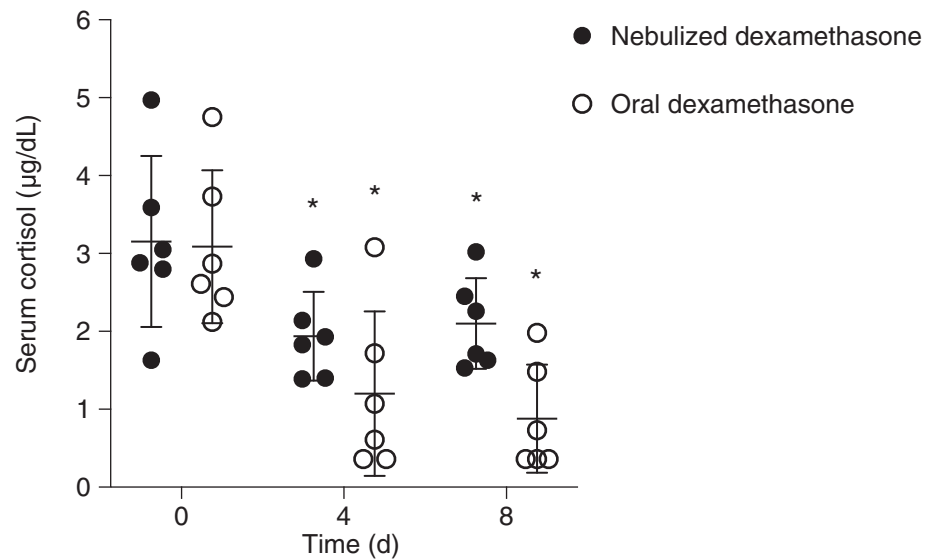
FIGURE 2 Transpulmonary pressure (P_L ; A), lung resistance (R_L ; B) and lung elastance (E_L ; C) (the horizontal lines represent the mean \pm SD) before and 10 minutes after administration of N-butylscopolammonium IV (0.03 mg/kg) on day 8 to horses with severe asthma treated with nebulized (black circles; $n = 6$) or PO (white circles; $n = 6$) dexamethasone (5 mg q24h). The dotted line represents values expected from healthy horses. * represents significant difference from baseline

more effective in the central airways,¹⁷ fewer drug particles may reach the more distal lungs with a higher amount eventually being swallowed and absorbed by the gastrointestinal tract.^{17,19} Most corticosteroids developed for inhalation have low PO bioavailability, resulting in decreased systemic absorption in asthmatic patients compared with healthy subjects.^{17,19} Liver metabolism also decreases serum half-life and systemic concentrations.²⁰⁻²² The cortisol suppression we observed may be a result of the higher PO bioavailability of dexamethasone solution (31-42%)⁸ compared to budesonide (11%) or fluticasone (< 1%),^{22,23} resulting in increased systemic absorption in horses with asthma. However, PO bioavailability is not the only variable affecting systemic absorption. It was also hypothesized that

disease state and disease severity may affect inhaled corticosteroid uptake differentially, depending on their solubility and other characteristics.¹⁷ Another hypothesis for increased systemic absorption of corticosteroids is that the inflamed epithelium in the equine airways may have higher absorption capacity than normal epithelium.^{24,25} Thus, consequences of asthma on lung absorption of corticosteroids may differ among drugs, potentially contributing to the discrepancies among the results of the different studies.

In our study, if the effect of nebulized dexamethasone was a consequence of systemic absorption, the low dose and the formulation used may account for the absence of lung function improvement. Indeed, doses reported effective in horses with asthma are at least

FIGURE 3 Concentration of serum cortisol at baseline, on day 4 and day 8 (the horizontal lines represent the mean \pm SD) in horses with severe asthma treated with nebulized (black circles; $n = 6$) or PO (white circles; $n = 6$) dexamethasone (5 mg q24h). * represents significant difference from baseline



5 times the amount used in our study,²⁶⁻²⁸ and gastrointestinal absorption after PO administration of injectable dexamethasone could be lower than powder formulations for PO use (fasted horses).⁸ Our results are in agreement with a study that reported that a low dose (0.02 mg/kg) of the same formulation of injectable dexamethasone only mildly improved lung function of horses with asthma.²⁹ The lack of improvement in our NE group, compared to the mild improvement of lung function in the OR group, may be the result of a smaller amount of drug reaching the gastrointestinal tract when dexamethasone is nebulized, whereas the remainder finally reaches the central airways or is lost in the nebulization device or in nasal discharges. The dose of dexamethasone (5 mg) selected for our study was chosen for comparative purposes with previous published reports.^{13,14} This dose may have been too low to be effective in horses with asthma but, although higher dosages may result in lung function improvement, suppression of the hypothalamo-pituitary-adrenal axis could negate the advantages of the inhaled route. Furthermore, with higher doses, because both the PO and nebulized routes would have resulted in improved lung function,²⁹ it would not have been possible to determine the contribution of lung deposition and absorption of the drug on the effects observed.

The decreased serum cortisol concentrations were not significantly different between groups. However, contrary to NE group, raw data for OR group were under the normal serum cortisol concentration reference limit for all about 1 horse, and half of the horses had results below the limit of detection. Oral administration seemed to induce more HPA suppression than nebulized dexamethasone, reinforcing the suspicion of a lesser amounts of drug reaching the gastrointestinal tract when dexamethasone is nebulized. This decrease in serum cortisol concentration is consistent with previous studies after 7 days of PO (0.05 mg/kg, oral powder),²⁷ IV (0.04 mg/kg),³⁰ or as soon as after 2 days of PO administration of a low dose (0.02 mg/kg) of injectable dexamethasone in combination with theophylline.²⁹ Most inhaled corticosteroids studied in horses with asthma (eg, fluticasone,⁹ budesonide²⁸) also suppress serum cortisol

concentrations at dosages required to improve lung function. Inhaled ciclesonide currently is the only effective inhaled corticosteroid tested in horses that is not associated with serum cortisol concentration suppression.³¹ Although cortisol suppression has not yet been shown to have clinical consequences in horses, it indicates that systemic effects²² potentially can be health threatening.³²

Our study had several limitations. First, hay was given at 5:00 PM and even if no hay usually remained in the horses' stalls at the time of dexamethasone administration (7:00-8:00 AM), variability in dexamethasone absorption could have occurred because of an uncontrolled period of fasting. Moreover, horses were fed <30 minutes after drug administration. The absence of a predetermined fasting period before and after dexamethasone administration could have decreased its PO absorption, as reported in previous studies.^{8,26} Nevertheless, this protocol was implemented because it reflects field conditions.

Few horses (12) were studied as in previous reports.^{28,30} Six horses per treatment group allowed identification of clinical improvement after treatment with corticosteroids for severe asthma. To be clinically useful, we considered that a similar magnitude in the response to nebulized dexamethasone would be needed. However, the low number of horses partially can explain the lack of significant results, because 18 horses per group would have been needed to show a significant effect of treatment on respiratory function parameters in 80% of trials. Improved lung function with dexamethasone and the small sample size also could explain the lack of significant effect of the bronchodilator on lung parameters in the OR group. An irreversible pulmonary condition is unlikely because these horses are from an experimental herd and airway obstruction was reversible in previous^{14,31} and follow-up studies (unpublished data).

To conclude, the absence of improvement with nebulized dexamethasone in our study is in agreement with the previous report using a different nebulizer.¹⁴ Both studies show that this treatment modality is not effective for horses with severe asthma and does not offer an advantage over systemically-administered dexamethasone. The characteristics of the injectable dexamethasone solution studied could

make it less suitable for nebulization. Whether increasing the dose or frequency would provide further patient benefit is unknown, but the lack of efficacy and suppression of serum cortisol concentrations observed with nebulized dexamethasone do not support use of this treatment modality for horses with severe asthma.

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CONFLICT OF INTEREST DECLARATION

Nortev provided funding and equipment for this experiment.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was performed at the Faculty of Veterinary Medicine of the University of Montreal. All experimental procedures were approved by the Animal Care Committee of the Faculty of Veterinary Medicine of the University of Montreal (protocol #18-Rech-1935).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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