Efficacy of dexamethasone, salbutamol, and reduced respirable particulate concentration on aerobic capacity in horses with smoke-induced mild asthma

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Abstract

Background: Mild asthma in horses decreases racing performance and impairs gas exchange. The efficacy of treatment on performance is unknown.

Hypothesis: Treatment targeting lung inflammation improves VO2peak in horses with mild asthma.

Animals: Thoroughbred polo horses (n = 12) with smoke-induced mild asthma. Horses were exposed to increased ambient particulate matter (35.51 μg/m³ [PM2.5]; day mean, centrally measured) from day −33 to 0, from bushfire smoke (natural model).

Methods: Prospective, randomized, placebo-controlled, double-blinded clinical trial. All horses completed 3 VO2peak tests, measuring aerobic and anaerobic variables: day 0 -baseline; day 16 -after dexamethasone (20 mg IM q24h; DEX, n = 6) or saline treatment (SALINE, n = 6), under improved ambient PM2.5 concentrations (7.04 μg/m³); day 17-15-30mins after inhaled salbutamol (1500 μg). Bronchoalveolar lavage and mucus scoring were performed on day −8 and day 20. Linear mixed effects models were used to examine the effects of timepoint and treatment group on BAL differential cell counts, mucus scores, aerobic and anaerobic variables.

Results: Horses’ mucus scores improved significantly from day −8 to 20 by 1.27 ± .38 (P = .01). There was a significant increase in VO2peak of 15.5 ± 4.0 mL/(min.kg)−1 from day 0 to 17 (P = .002), representing an average (mean) increase in VO2peak of 13.2%. There was no difference in VO2peak between treatment groups (SALINE versus DEX) at any timepoint.

Conclusions and Clinical Importance: This study highlighted the key role of improved air quality on functionally important airway inflammation. Evidence provided is central to increasing owner compliance regarding improved air quality for the treatment and prevention of mild asthma.
INTRODUCTION

Mild asthma in horses decreases racing performance in Thoroughbred racehorses. Furthermore, in studies performed in a controlled environment on a high-speed treadmill gas exchange is impaired after exercise in horses with mild asthma. Therefore, given that one of the presenting complaints of mild asthma is poor performance, evidence regarding the efficacy of treatment on performance and aerobic capacity would be valuable.

Horses with mild asthma have empirically been treated with glucocorticoids. Dexamethasone (0.05 mg/kg IM q24h) and inhaled fluticasone (3000 μg q12h) are effective at reducing hypersensitivity and hyperreactivity in horses with mild asthma. However, no improvement in bronchoalveolar lavage (BAL) neutrophil percentage was observed after short-term administration of glucocorticoids, which is consistent with findings in severe asthma studies where the air quality was not improved. Interestingly, without environmental modification long-term dexamethasone and fluticasone administration have no effect on airway neutrophilia, even after 6 to 7 months. However, when corticosteroid treatment is combined with measures to improve air quality it improves clinical signs, airway neutrophilia and inflammatory cytokines in horses with severe asthma. Excessive tracheal mucus accumulation is a feature of mild asthma, and increased mucociliary clearance might be also be beneficial in the amelioration of the condition. Airway hyperresponsiveness is also observed in horses with mild asthma, and is associated with respiratory clinical signs and exercise intolerance. Airway hyperresponsiveness is often treated with an inhaled bronchodilator; however, the degree of bronchoconstriction in horses with mild asthma does not increase respiratory effort at rest and its effect on exercise capacity is not well documented. Treatment with bronchodilators should always be in conjunction with environmental control strategies to reduce exposure to dust to ensure that the amount of particulates reaching the lower airways is not increased.

The aerobic capacity of a horse can be directly measured as maximal oxygen consumption (VO₂max). Typically, VO₂max is characterized by demonstrating no increase in VO₂ despite an increase in workload. Under field conditions, this can be difficult to demonstrate conclusively with the result that the variable VO₂peak is often preferred. Traditionally, VO₂ has been measured in equine sports medicine using stationary equipment under laboratory conditions, while a horse performs a standardized treadmill incremental speed test. A major limitation of these laboratory tests is the fact that they do not reflect exercise performed under genuine field conditions. Attempts have been made to measure VO₂peak in the field in horses. Increased resistance to airflow induced by the masks required by the procedure renders the VO₂peak measurements unreliable and presented unacceptable risks to the horses. Recently a mask has been developed and validated that can accurately measure VO₂peak, airflows, and tidal volumes on a breath-by-breath basis under field conditions.

The overall aim of our study was to evaluate the hypothesis that treatment targeting lung inflammation improves VO₂peak in horses with mild asthma. Our specific objective was to determine whether dexamethasone, salbutamol, and a reduction in ambient PM2.5 increase VO₂peak in the field in horses with mild asthma.

MATERIALS AND METHODS

2.1 Horse enrollment and study design

This was a prospective, randomized, controlled, double-blinded clinical trial. Argentinean Thoroughbred horses (n = 12; 10 mares, 2 geldings; 6-17 years old; mean weight 493 ± 26 kg) used for polo were recruited at the end of the competition season when horses were at a maintenance level of fitness. All horses continued their maintenance exercise regime throughout the trial to ensure no deconditioning occurred (5-10-minute walk, 15-20 minutes canter/extended trot, 15-minute walk, turned out; 5-6 days/week). Air quality was poor due to bushfire smoke for 1 month prior to the initial peak exercise test (day 0; Figure 1), with an average daily ambient particulate mass < 2.5 μm (PM2.5) of 35.51 μg/m³ from day −33 to day 0. Air quality improved on day 0, with an average daily value of 7.04 μg/m³ (PM2.5) from day 0 to day 20. This average approved air quality data was centrally measured and obtained from the City of Calgary under the Open Government License. Horses had a history of coughing and decreased performance during the period of exposure to smoke and resided on 2 properties in close proximity to each other. Of the 12 horses, 10 were turned out together in a 30-acre grass paddock; the other 2 horses were kept outside in a smaller grass/dirt paddock at the polo club. Except for clinical signs consistent with mild asthma, horses were judged to be healthy based on thorough physical, lameness, and respiratory examinations. All horses were reported to have had no history of general health issues or respiratory infections during the previous polo season. For the

Day-0: Performance testing (T1)  Day 0: BAL and scope
Day 120: Treatment (DEX/SALINE) Day 16: Performance testing (T2)
Day 17: Performance testing with bronchodilator (T3)  Day 20: BAL and scope

FIGURE 1 Representation of protocol and treatment group allocation. Horses were randomly allocated into 2 treatment groups, DEX (n = 6) and SALINE (n = 6).
duration of the trial, the horses’ diet consisted of pasture supplemented with senior feed, with alfalfa hay also being provided (spread out on ground) for the 2 horses housed at the polo club. BAL fluid was obtained from all horses (n = 12), and respiratory endoscopy (Karl Storz Endoscope, Mississauga, ON, Canada) was performed for mucus scoring twice, on day –8 and day 20 (Figure 1). On day –7, horses were randomly allocated into 1 of 2 treatment groups: DEX (horses treated with 20 mg dexamethasone IM SID; n = 6) and SALINE (horses treated with 4 mL saline IM SID; n = 6). The person administering the treatments and performing the respiratory and statistical analysis was blinded to the treatment groups. All horses had chronic coughs and were considered to have smoke-induced mild asthma based on the following inclusion criteria (defined in a consensus publication): (a) a BAL with increased percentage of mast cells (> 2%) or/and eosinophils (> 0.5%) or/and neutrophils (> 5%); (b) history of coughing and poor performance; and (c) absence of labored breathing at rest. On day 0 (Figure 1), horses completed their first VO2peak test. Treatment commenced on day 1. VO2peak was measured again on day 16. On day 17, horses were administered salbutamol (1500 μg) 13 to 30 minutes prior to completing their third peak exercise test (Figure 1). Ambient temperature ranged from 19°C to 20°C (day 0), 5°C to 9°C (day 16), and 3°C to 6°C (day 17). As exercise in cold conditions has been shown to induce a transient airway neutrophilia and is associated with higher respiratory impedance and resistance 48 hours after exercise, horses were given 3 days to recover from the runs prior to the BAL and scoping procedure being repeated on day 20 (Figure 1). Horses were treated for 20 days, from day 1 until day 20.

2.2 Procedures

Horses were sedated to effect with xylazine hydrochloride (0.4-0.5 mg/kg, IV) and butorphanol tartrate (0.05-0.1 mg/kg, IV). Horses were then endoscopically scored for tracheal mucus (Karl Storz, Mississauga, ON, Canada). A blind BAL was then performed as previously described. Lavage fluid was stored immediately after collection at 4°C. Preparation of slides was performed within 6 hours of sample collection using 400 μL of BAL fluid, which was centrifuged using a Cytospin (900 μL for 5 minutes) and stained with modified Wright-Giemsa stain. A differential cell count was performed on a minimum of 2000 cells by a board-certified pathologist. Epithelial cells were not included in the differential count.

2.3 Peak exercise test

Horses performed a maximal intensity exercise test on a 4-furlong (804.7 m) sand track located at BarNone Ranch, AB, Canada. Horses completed a standardized warm-up that consisted of an 800 m trot and 800 m canter. A mask capable of accurately measuring VO2peak, airflow, and tidal volume on a breath-by-breath basis under field conditions was then applied, and horses completed 400 m at a canter followed by 600 m at maximal intensity. Calibration of the system (flowmeter and gas analyzer) was conducted as previously reported before and after each horse was exercised. The mask was internally padded and adjusted for each horse to minimize dead space. Results (including run duration) were calculated using customized software provided with the system. Environmental conditions (ambient temperature, barometric pressure and humidity) were recorded and included in ventilation calculations. Horse weight was collected (Horse Weigh, Powys, Wales) prior to each exercise test and included in VO2peak calculations. Results are reported as STPD (standard temperature and pressure, dry).

Jugular venous blood samples (2 mL) were collected in lithium-heparin containing vacutainer tubes at rest, and 5, 10, and 15 minutes postexercise to ensure peak blood lactate concentration was obtained. A handheld analyzer (Lactate Scout+, EKF Diagnostics, Penarth, Wales) was used to immediately measure the blood lactate concentration.

Heart rate (HR) was monitored continuously during exercise using a telemetric ECG device and software (Televet 100, Engel Engineering Service, Heusenstamm, Germany). A base/apex configuration was used. Tracings were analyzed to ensure HR plateaued, indicating a maximal effort was obtained.

The aerobic contribution to the metabolic energy consumed during the exercise test was calculated using the trapezoidal method (subtracting resting O2 consumption). Resting and peak blood lactate were recorded. Lactate anaerobic contribution was calculated by multiplying the ΔBLPeak-Resting by 3 as previously described using this estimation method in human subjects and horses. Calculated contributions (mL) were then converted into kJ (1 L O2 = 20.92 kJ) to determine the relative contributions.

2.4 Statistical analysis

Normality of the distribution of the BALF differential cell counts were tested by a Shapiro–Wilks normality test. Linear mixed effects models were used to examine the effects of timepoint (day 0, day 16, and day 17, Figure 1) and treatment group (DEX and SALINE) (as fixed effects) on BALF differential cell counts, mucus scores, and anaerobic and anaerobic variables outlined in Table 1 (as the outcomes), after accounting for the nested data structure from horses (as a random effect). The assumptions of normality and equal variance were assessed. Analysis was performed using R version 3.4.1, and “nlme” package version 3.1-137 was used for linear mixed effects model analysis. Statistical significance was set at P ≤ .05 for all tests. Values are reported as mean ± SD except where stated as median and interquartile range (IQR) to accommodate non-normal data.

3 RESULTS

3.1 Cytology

Bronchoalveolar lavage fluid differential cell counts for each treatment group on day –8 and day 20 are shown in Figure 2. The proportion of alveolar macrophages in the BAL fluid significantly increased by 10.8%
Horses; Figure S2). Epithelial cells were very rare or absent and were observed on both day 8 and day 20. There was no significant difference in the proportion of any cell type between treatment groups (neutrophils: \( P = .34 \); mast cells: \( P = .09 \); alveolar macrophages: \( P = .92 \); lymphocytes: \( P = .66 \)). Abundant extracellular debris and pollen were present in every BAL on both day 8 and day 20, with some horses also displaying evidence of erythrophagocytosis (Figure S1). Cushing’s spirals were observed on both day 8 (2 horses) and day 20 (2 different horses; Figure S2). Epithelial cells were very rare or absent and were always ciliated.

### 3.2 | Mucus scoring

On day 8, the median (IQR) mucus score of horses was 1.5 (5-3) (SALINE) and 1 (63-2.5) (DEX). On day 20, the median mucus score was 0.25 (0-88) (SALINE) and 0 (0-0) (DEX).

Horses’ mucus score improved significantly from day 8 to day 20 by 1.27 ± .38 \( (P = .01) \). There was no difference in mucus score between treatment groups \( (P = .44) \).

### 3.3 | Peak exercise test

For descriptive values for aerobic and anaerobic variables measured and calculated for both treatment groups before treatment (day 0), after treatment with dexamethasone or a saline control (day 16) and with the addition of inhaled salbutamol <30 minutes prior to the peak exercise test (day 17), see Table 1. Heart rate data for each run was analyzed to ensure a plateau was reached (data not shown).

Horses were 6.7 kg ± 1.9 kg heavier at day 0 than at day 16 and day 17 \( (P = .002) \); there was no difference in weight between day 16 and day 17. There was no difference in weight between treatment groups \( (P = .72) \) at any timepoint.

Horses were significantly faster at day 16 and day 17 than at day 0, with the overall run duration decreasing from day 0 by 6.6 seconds ± 1.4 seconds at day 16 \( (P = .001) \), and by 3.9 seconds ± 1.3 seconds at day 17 \( (P = .01) \), respectively. There was no significant difference in overall run duration between day 16 and day 17 \( (P = .1) \). There was no significant difference in overall run duration between treatment groups \( (P = .3) \).

There was a significant increase in \( \text{VO}_2\text{peak} \) of 15.5 ± 4.0 mL\( \text{(kg.min)}^{-1} \) from day 0 to day 17 \( (P = .002) \). There was a nonsignificant increase in \( \text{VO}_2\text{peak} \) of 6.3 ± 4.5 mL\( \text{(kg.min)}^{-1} \) from day 0 to day 16 \( (P = .19) \). There was also a near-significant increase in \( \text{VO}_2\text{peak} \) of 9.2 ± 4.7 mL\( \text{(kg.min)}^{-1} \) from day 16 to day 17 \( (P = .07) \). There was no significant difference between treatment groups at any timepoint \( (P = .91) \).

There was no difference in peak lactate between day 0 and day 16 \( (P = .77) \), day 0 and day 17 \( (P = .13) \), or day 16 and day 17 \( (P = .22) \) (Table 1). There was no difference in peak lactate between treatment groups at any timepoint \( (P = .78) \).

There was no difference in total exercise aerobic \( (P = .88) \) or anaerobic \( (P = .49) \) energy \( (\text{kJ}) \) between treatment groups. There was no significant difference in total exercise aerobic or anaerobic energy between any timepoints (aerobic: day 0 and day 16 \( (P = .18) \), day 0 and day 17 \( (P = .38) \), day 16 and day 17 \( (P = .05) \); anaerobic: day 0 and day 16 \( (P = .88) \), day 0 and day 17 \( (P = .35) \), or day 16 and day 17 \( (P = .28) \) (Table 1). Consequently there was no difference in aerobic or anaerobic contributions to total energy production \( (\%) \) between treatment groups \( (P = .82) \) at any timepoint.
The single most important factor in the enhanced aerobic capacity seen in these horses with mild asthma appeared to be improved environmental conditions as documented by significantly decreased ambient PM$_{2.5}$ measures. Dexamethasone administration was not associated with any additional benefit over a reduction in ambient PM$_{2.5}$ alone, on any measured or calculated variable. VO$_2$peak significantly increased between day 0 and day 16, presumably due to vastly improved ambient particulate concentrations during this period, and the addition of salbutamol administration did not affect VO$_2$peak, regardless of dexamethasone treatment. Reduced ambient PM$_{2.5}$ was associated with a significant decrease in overall run time and correspondingly, increased speed. Horses’ mucus scores significantly improved by a mean of 1.27 from day −8 to day 20. The proportion of eosinophils in BAL fluid decreased by 0.79% from day −8 to day 20; there was no change in the proportion of neutrophils or mast cells. There was no significant difference in the proportion of any cell type between horses treated with dexamethasone and saline.

There were multiple challenges associated with the execution of the original study design, including uncontrollable factors requiring extension of the sampling timepoints; day 0 was delayed after the initial BAL and mucus scoring due to ergospirometry mask repairs. An advantage of the study design was a longer study duration that allowed additional time for clearance of inflammatory cells from the lungs, and improvement in respiratory performance.

Moderate to severe tracheal mucus (grades 2-4)$^{22}$ is a risk factor for poor racing performance in racing Thoroughbreds, based on race place closest to the time of sampling, and whether the horse was raced within 2 weeks of sampling.$^{33}$ Tracheal mucus accumulation and not an increased proportion of tracheal neutrophil, is associated with functionally important airway inflammation.$^{33}$ It is important to note that tracheal mucus is positively correlated with BAL neutrophilia in some studies,$^{34}$ but not others.$^{35-37}$ Prior to treatment the median mucus score of horses in the present study was 1-1.5 depending on treatment group. Whilst this was below the score previously associated with poor racing performance, this level of airway inflammation was associated with clinical signs of coughing and poor performance. The increased sensitivity of the methods employed in the present study where performance was directly measured as the horses’ peak oxygen consumption and speed, found a significant average improvement in VO$_2$peak of 13.2% from day 0 to day 17, with horses improving in mucus score by a mean of 1.27 grades.

There is strong evidence that corticosteroid therapy does not normalize airway neutrophilia without environmental modifications, even after treatment periods of up to 6 months.$^{6,10,38-40}$ when corticosteroid treatment is combined with measures to improve air quality an improvement in clinical signs, improvement in airway neutrophilia and inflammatory cytokine expression is observed in horses with severe asthma.$^{10,11}$ It is possible that longer treatment periods are required to achieve resolution of airway neutrophilia following prolonged exposure to poor ambient air quality. Indeed, smoke inhalation is known to disrupt mucociliary clearance, with 5 minutes of cigarette smoke resulting in a marked loss of ciliated cells from the bronchial luminal surface.$^{41}$ The effects of chronic smoke inhalation on the equine respiratory tract have not been studied; however, it is plausible that normalization of airway neutrophilia could be extended after damage to the mucociliary apparatus and other deleterious effects of smoke exposure. Whereas the authors are unaware of a reported link between chronic smoke inhalation from bushfires and mild asthma in horses, there is strong evidence linking development of airway inflammation with exposure to higher dust environs.$^{42-44}$ Given that horses had no history of coughing, poor performance, or respiratory disease in the polo season prior to the deterioration of air quality associated with bushfire smoke, and that exposure to higher levels of respirable particulate matter coincided with the

**FIGURE 2** Bronchoalveolar lavage fluid differential cell count percentages (n = 12 horses) for each treatment group DEX (n = 6) and SALINE (n = 6) on day −8 (gray bars) and day 20 (white bars). A, Neutrophil percentage. B, Mast cells percentage. C, Eosinophils percentage. D, Macrophages percentage. E, Lymphocytes percentage. Median and individual data shown

### 4 | DISCUSSION

The single most important factor in the enhanced aerobic capacity seen in these horses with mild asthma appeared to be improved environmental conditions as documented by significantly decreased ambient PM$_{2.5}$ measures. Dexamethasone administration was not associated with any additional benefit over a reduction in ambient PM$_{2.5}$ alone, on any measured or calculated variable. VO$_2$peak significantly increased between day 0 and day 16, presumably due to vastly improved ambient particulate concentrations during this period, and the addition of salbutamol administration did not affect VO$_2$peak, regardless of dexamethasone treatment. Reduced ambient PM$_{2.5}$ was associated with a significant decrease in overall run time and correspondingly, increased speed. Horses’ mucus scores significantly improved by a mean of 1.27 from day −8 to day 20. The proportion of eosinophils in BAL fluid decreased by 0.79% from day −8 to day 20; there was no change in the proportion of neutrophils or mast cells. There was no significant difference in the proportion of any cell type between horses treated with dexamethasone and saline.

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onset of clinical signs, it is likely that the fact that 100% of horses in the study had both the clinical signs and lesions of mild asthma was associated with chronic smoke exposure.

In elite nonasthmatic human athletes and mild asthmatics, salbutamol administration does not significantly affect VO₂peak. However, it does increase FEV₁ (mean forced expiratory volume in 1 second) both at baseline and after exercise. This agrees with after exercise findings in both healthy horses (albuterol and clenbuterol), and those with severe asthma after bronchodilator administration (ipratropium bromide); it would appear that maximal sympathetic drive associated with exercise overrides any pharmacologic benefits conferred at rest. In contrast, bronchodilator treatment had a significant effect (121.7 mL(min.kg)⁻¹ versus 130.3 mL(min.kg)⁻¹ in horses treated with a placebo and inhaled albuterol, respectively) on VO₂peak in fit Thoroughbred horses.

We found that salbutamol administration did not result in a significant difference in VO₂peak compared to an improvement in air quality, with and without dexamethasone administration. However, there was a nonsignificant increase in VO₂peak after salbutamol administration, and it is possible that we did not have enough power to detect a difference. Alternatively, horses might have had a greater understanding of what the jockey required of them; this improvement could represent a learned response to a repeated situation. Additional benefits of bronchodilators include increased mucociliary clearance, anti-inflammatory properties, and at higher doses, some human patients with chronic obstructive pulmonary disease exhibit improved exercise tolerance without concurrent improvement in airflow, attributed to increased diaphragmatic contractility. Effects of bronchodilator therapy on equine respiratory muscles have not been investigated.

This study highlights the importance of improved air quality on functionally significant airway inflammation. Dexamethasone administration was not associated with any additional benefit over a reduction in ambient PM₂.₅ alone (ie, no difference between the control group and the group administered dexamethasone) on any measured or calculated variable. Improved ambient air quality was associated with a significant increase in VO₂peak of an average 13.2%. Mild asthma affects up to 66% of horses at some time in their lives, with 100% of horses in the present study being affected by bushfire smoke. However, owner compliance with veterinary recommendations, particularly regarding improving environmental management and limiting exposure to dust, is poor, with medical treatment being the preferred option for many clients. Therefore, the evidence regarding the corrective efficacy of treatment provided herein is central to increasing owner compliance with veterinary recommendations and thus improving not only the welfare, but also the performance of a large proportion of the equine population.