

Environment and prednisone interactions in the treatment of recurrent airway obstruction (heaves)

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Summary

Recurrent airway obstruction (RAO) or heaves is a manifestation of a hypersensitivity to dust, moulds, and spores in the environment of a susceptible horse. Although in the majority of RAO-affected horses, clinical remission can be achieved by keeping horses at pasture to reduce their allergen exposure, this often is not practicable. For this reason, we investigated if changing the environment of a single stall in a 4 stall stable was sufficient to improve lung function and reduce inflammation in RAO-affected horses. In addition, we determined if addition of oral prednisone provided additional benefit. Twelve RAO-susceptible horses were stabled, fed hay, and bedded on straw until they developed airway obstruction. At this point, bedding was changed to wood shavings and they were fed a pelleted diet for 2 weeks. Lung function was measured and bronchoalveolar lavage was performed before and 3, 7, and 14 days after environmental modification. In a crossover design, horses were treated for the 14 days with prednisone tablets (2.2 mg/kg bwt, q. 24 h). Horses then returned to pasture for 30 days. Airway obstruction was greatest before environmental modification. Significant improvement in lung function occurred within 3 days of the change in environment and continued to Day 7. Airway function was best after 30 days at pasture. The clinical response achieved by environmental modification was not significantly improved by addition of oral prednisone. The total number of cells, total neutrophils, and percent neutrophils was greatest before environmental modification. In the absence of prednisone, total and percent neutrophils did not decrease until Day 14 and total cell number until 30 days at pasture. In the presence of prednisone, total cells and total and percent neutrophils decreased by Day 3 and again at pasture. The fact that lung function can be improved within 3 days by environmental management alone emphasises the need for allergen reduction as the cornerstone of treatment of RAO. Although prednisone induced a more rapid reduction in airway inflammation, this was not associated with a more rapid improvement in airway function.

Introduction

Recurrent airway obstruction (RAO), also known as heaves, is a form of the syndrome known as equine chronic obstructive pulmonary disease (COPD) and is a hypersensitivity to the dust,

molds, and spores in the horse's environment (Halliwell *et al.* 1993). This hypersensitivity leads to bronchoconstriction, accumulation of mucoid secretions in the airways, and mural inflammation that culminates in airway obstruction (Robinson *et al.* 1996). In the majority of horses afflicted with RAO, the airway obstruction is in part reversible with environmental management to reduce antigen exposure. Significant reduction in antigen exposure requires a decrease in the concentration of dust and particulate matter in the area immediately around the horse's face, i.e. in its breathing zone (Woods *et al.* 1993). This often requires the RAO-susceptible horse to be kept at pasture and have hay removed from the diet, a management practice that is difficult for many horse owners to accept or implement.

Corticosteroids often are incorporated into the treatment of horses with RAO when complete environmental modification proves impossible. The potent steroids have been demonstrated to be effective medications. For example, a single dose of triamcinolone acetonide (0.09 mg/kg bwt i.m.) improves lung function for several weeks (LaPointe *et al.* 1993). Dexamethasone (0.1 mg/kg bwt i.v. q. 24 h) relieves airway obstruction after 3 days in stabled RAO-affected horses maintained on mouldy hay and straw (Rush *et al.* 1998a, b). However, despite its widespread use, there is no documentation of the therapeutic value of oral prednisone. In the only published study, administration of an oral dose (400 mg/horse, q. 24 h) for 10 days failed significantly to improve clinical signs of COPD or to alter neutrophil counts in bronchoalveolar lavage (BAL) fluid (Traub-Dargatz *et al.* 1992).

A serious consideration in the use of parenterally administered corticosteroids is their association with adverse systemic effects (Rush *et al.* 1998c). It therefore becomes important for the practitioner to have an appreciation of the clinical response that can be achieved by solely modifying the immediate environment of an RAO-susceptible horse and if that response is augmented through the use of systemic corticosteroids. The purpose of the present study was to determine if modifying conditions in the stall of an RAO-affected horse, while maintaining standard conditions of management in the rest of the stable, was sufficient to improve pulmonary function or alter the BAL cell population. We also investigated if the administration of oral prednisone provided additional benefit above that achieved by modifying the conditions in a single stall. The role of bronchospasm in residual airway obstruction was also examined.

Materials and methods

Horses

Twelve horses (4 geldings, 8 mares) age 10–28 years of age with inducible airway obstruction were used in this study. Prior to the initiation of the experimental protocol, horses were maintained at pasture and fed a complete pelleted feed until they were in clinical remission. Horses were then housed in stalls, bedded on straw, and fed mouldy hay until they exhibited characteristic clinical signs of heaves. Lung function was measured at this time. Atropine (0.02 mg/kg bwt i.v.) was administered and, after 15 min, measurement of lung function was repeated to verify the reversibility of the airway obstruction. Horses were then returned to pasture for at least 30 days.

The stable

The stable was a 17 x 23 m metal building with three 3 x 3 m overhead doors and no windows. There were four 3.5 x 3.5 m wooden stalls along one wall. The walls of the stalls were 2.3 m high and were solid on 3 sides. At the front, the walls were solid for the lower 1.7 m and were barred for the remainder of their height. There was no roof on the stalls. The hay rack and manger were 1 and 1.5 m from the floor, respectively. Stalls were fitted with automatic waterers. Hay, straw, and other supplies were stored beside the last stall in the row. Stalls were cleaned once daily in the morning and the stable floor was swept daily.

During the experiment, management of a single stall was changed. Straw bedding was replaced by pine shavings and hay was replaced by a complete pelleted feed (Equine Senior)¹. Horses in the remaining 3 stalls continued to be fed hay and were bedded on straw. The doors of the stable were opened as needed for cleaning or to provide additional ventilation. The doors were a minimum of 5 m from the nearest stall.

Study design

This study was conducted during the summer and fall of 1998. It used a crossover design with 2 treatments, and horses were assigned randomly to the initial treatment. Treatments consisted of either environmental management alone or environmental management coupled with prednisone administration (2.2 mg/kg bwt *per os* q. 24 h). Prednisone tablets (Deltasone)², were crushed,

mixed in molasses and water and administered in the morning.

Figure 1 diagrams the time line of our investigation. At the start of the experiment, horses were at pasture and in clinical remission. They were brought from the pasture and housed in one of the 4 stalls. Initially, horses were bedded on straw, and fed mouldy hay until they began to show clinical signs of lower airway obstruction. The study began when the airway obstruction resulted in a maximal change in pleural pressure ($\Delta P_{pl_{max}}$) during tidal breathing of at least 25 cmH₂O. At this time, the baseline (Day 0) measurement of lung function was made and BAL was performed. The environmental management of the stall was then initiated as described above. These management changes were maintained for the remainder of the 14 day housing period.

Lung function measurement and BAL were repeated on days 3, 7, and 14. On days 7 and 14, the presence of bronchospasm was evaluated. Lung function was measured before and 15 minutes after administration of atropine (0.02 mg/kg bwt i.v.). Horses were then returned to pasture. After horses received prednisone, they were administered a halving dose of the drug every other day for 3 treatments. After 30 days at pasture (Day 44), lung function measurements and BAL were repeated. Horses were then returned to pasture for at least 7 days before returning to the stable for the other treatment. The study design was approved by the All-University Animal Use and Care Committee of Michigan State University.

Measurement of lung function

Pleural pressure was estimated by the use of a latex oesophageal balloon (10 cm long, 3.5 cm diameter, 0.6 mm thick) sealed over the distal end of a polypropylene catheter (3 mm inside diameter, 4.4 mm outside diameter, 240 cm long). The balloon was passed to the distal third of the oesophagus and connected to a pressure transducer (Model DP/45-35)³. Which was calibrated before each study by use of a water manometer. The position of the oesophageal balloon was adjusted to obtain the maximal $\Delta P_{pl_{max}}$ during a tidal breath. Flow rate was obtained using a pneumotachograph (No. 5 Fleisch)⁴ fitted in a face mask placed over the horse's muzzle and sealed with a rubber shroud and tape. The pneumotachograph was connected to a pressure transducer (DP/45-22), that provided a signal proportional to flow. The flow signal was passed to a pulmonary function

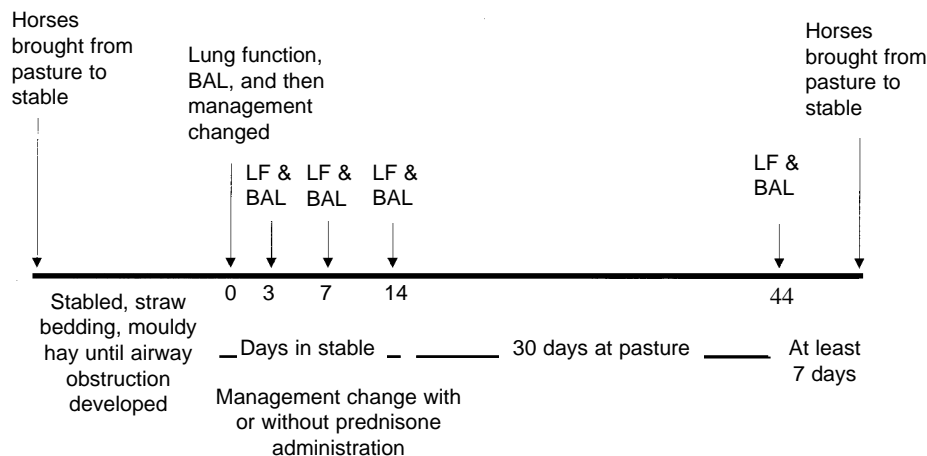


Fig 1: Time line showing the experimental design. The experiment was repeated with and without prednisone administration. LF = lung function measurement; BAL = bronchoalveolar lavage.

TABLE 1: Bronchoalveolar lavage fluid cytology

	Treatment	Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 44
Total cells per μl	1	371 ^b (247–556)	532 ^b (412–685)	253 ^b (188–340)	252 ^b (180–352)	84 ^a (59–118)
	2	575 ^b (348–933)	148 ^a (107–203)	240 ^b (167–348)	191 (121–299)	78 ^a (58–99)
Total neutrophils per μl	1	290 ^b (195–431)	290 ^b (191–443)	81 ^b (40–167)	76 ^{a,b} (41–139)	4 ^a (2–11)
	2	447 ^b (268–748)	50 ^{a,b} (31–81)	66 ^{a,b} (34–129)	50 ^{a,b} (29–85)	8 ^a (5–13)
Total lymphocytes per μl	1	8 ^b (5–13)	32 (20–50)	27 (19–38)	33 ^a (23–46)	17 ^a (11–27)
	2	10 (6–16)	17 (11–24)	13 (7–24)	19 (11–34)	14 (11–19)
Total macrophages per μl	1	52 (31–86)	91 (77–107)	53 (44–63)	55 (42–73)	36 (27–50)
	2	72 (43–119)	44 (34–58)	69 (52–92)	48 (25–93)	35 (27–46)
Percent neutrophils	1	79.5 \pm 3.8 ^b	64.1 \pm 7.8 ^{a,b}	55.2 \pm 9.1 ^{a,b}	50.4 \pm 10.3 ^{a,b}	21.2 \pm 6.8 ^a
	2	79.8 \pm 3.6 ^b	43.1 \pm 7.9 ^a	48.8 \pm 9.5 ^{a,b}	47.1 \pm 8.9 ^{a,b}	24.7 \pm 8.3 ^a
Percent lymphocytes	1	3.7 \pm 1.3 ^b	14.8 \pm 4.6 ^a	16.3 \pm 4.8 ^{a,b}	20.3 \pm 4.9 ^a	29.1 \pm 6.8 ^a
	2	4.9 \pm 1.5 ^b	19.3 \pm 4.3 ^a	13.8 \pm 4.1 ^{a,b}	16.1 \pm 6.5	23.3 \pm 4.8 ^a
Percent monocytes	1	16.8 \pm 3.1 ^b	21.2 \pm 4.4	28.5 \pm 6.8	29.3 \pm 6.1 ^a	49.5 \pm 7.2 ^a
	2	15.0 \pm 2.4 ^b	37.6 \pm 5.7 ^a	37.4 \pm 6.7 ^a	36.7 \pm 8.1 ^a	52.0 \pm 6.7 ^a

Treatment 1 = environmental management alone; Treatment 2 = environmental management plus prednisone. Values for percent cells represent mean \pm s.e. In the case of the total cell numbers, data were log transformed for analysis. Values in parentheses represent the range of mean \pm s.e. ^a = significantly different from Day 1; ^b = significantly different from Day 44.

computer, which integrated the signal to provide tidal volume. The pneumotachograph/transducer/computer system was calibrated by means of a 2 l syringe. Flow, tidal volume, and $\Delta\text{Ppl}_{\text{max}}$ during breathing were processed by the pulmonary function computer (Model LS 14)⁵, to provide breath-by-breath measurement of pulmonary resistance (R_L) and dynamic elastance (E_{dyn}). Thirty consecutive breaths were used to calculate R_L , E_{dyn} , and $\Delta\text{Ppl}_{\text{max}}$ at each data collection period.

Bronchoalveolar lavage

Horses were sedated with xylazine hydrochloride (0.2–0.4 mg/kg bwt i.v.) and restrained with a nose twitch. Bronchoalveolar lavage was performed by means of a 300 cm, 10 mm diameter BAL catheter with an inflatable cuff⁶ passed via the nose and wedged in a peripheral bronchus.

Three hundred millilitres phosphate-buffered saline⁷ was infused by hand in 100 ml aliquots and recovered by manual aspiration. The volume of BAL fluid (BALF) recovered was recorded and dithiothreitol⁸ added to a final concentration of 0.1% to disperse airway mucins. The sample was agitated vigorously for 15 min. Samples were centrifuged at 350 g at 4°C for 10 min. The BAL cellular pellet was washed 3 times and resuspended with 10 ml phosphate buffered saline. Total

nucleated cell counts were determined by use of a haemocytometer. Differential cell counts were determined by examination of 200 consecutive leucocytes on a cytocentrifuged cytologic preparation stained with Diff-Quick.

Statistical analysis

Results of pulmonary function measurements and BALF cytology were examined by a repeated-measures ANOVA with time (days of treatment) and treatment (environmental change alone or environmental change plus prednisone) as the main effects. Data on total cell numbers in BALF were log transformed before analysis. When there was a significant effect ($P < 0.05$) of time, contrasts were used to compare values at each time period. If there were significant interactions ($P < 0.1$) between main effects or at individual time intervals (as evaluated by contrasts), a repeated-measures ANOVA and appropriate contrasts were used to evaluate the effect of time in each treatment individually. Statistical analysis was performed using SPSS Version 7 for Windows.

Results

Modifying the immediate environment of RAO-affected horses

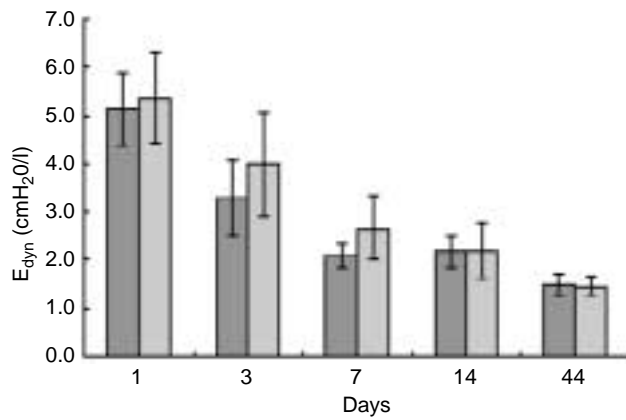


Fig 2: Effect of a change in environment (dark bars) and a change in environment coupled with prednisone treatment (light bars) on dynamic elastance (E_{dyn}) in horses with recurrent airway obstruction. See text for statistical information.

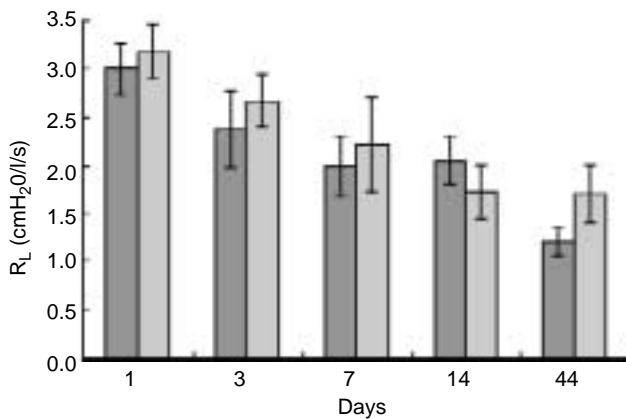


Fig 3: Effect of a change in environment (dark bars) and a change in environment coupled with prednisone treatment (light bars) on pulmonary resistance (R_L) in horses with recurrent airway obstruction. See text for statistical information.

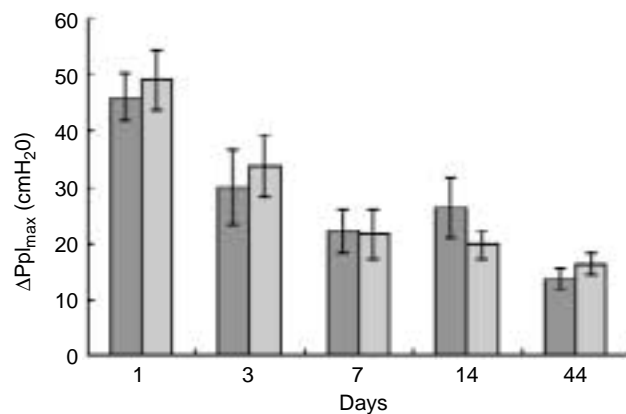


Fig 4: Effect of a change in environment (dark bars) and a change in environment coupled with prednisone treatment (light bars) on maximal change in pleural pressure (ΔPpl_{max}) in horses with recurrent airway obstruction. See text for statistical information.

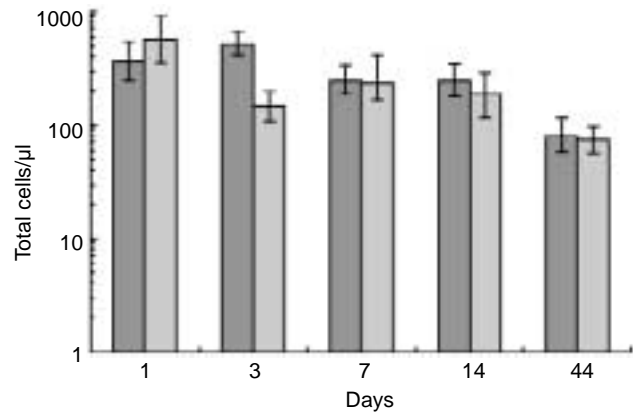


Fig 5: Effect of a change in environment (dark bars) and a change in environment coupled with prednisone treatment (light bars) on total cells in bronchoalveolar lavage fluid in horses with recurrent airway obstruction. See text for statistical information.

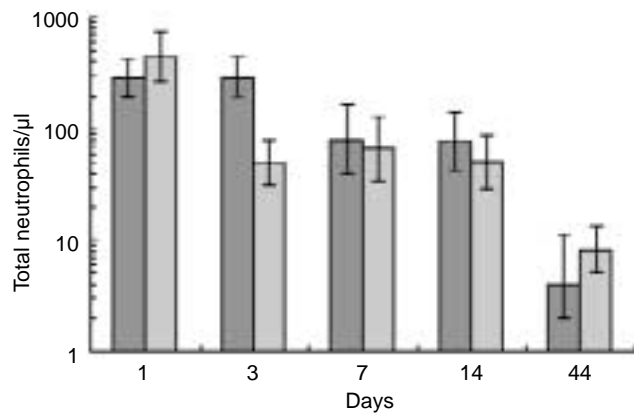


Fig 6: Effect of a change in environment (dark bars) and a change in environment coupled with prednisone treatment (light bars) on total neutrophils in bronchoalveolar fluid in horses with recurrent airway obstruction. See text for statistical information.

by changing their bedding to shavings and feeding exclusively a pelleted diet improved lung function within 3 days. The addition of oral prednisone provided no additional benefit.

At baseline (Day 1), R_L , E_{dyn} and ΔPpl_{max} were all increased to a level that indicated severe airway obstruction (Robinson *et al.* 1999) but there was no significant difference between the treatments at this time (Figs 2–4). There was a significant effect of time (environment) on E_{dyn} , R_L and ΔPpl_{max} , but no significant difference between the 2 treatments (prednisone/no prednisone) and no time/treatment interactions. In the case of E_{dyn} , a significant improvement occurred within 3 days of changing the environment, with a further improvement by Day 7. Even though mean E_{dyn} was least after horses had been at pasture for 30 days, this value was not significantly different from Day 7. Pulmonary resistance was significantly improved by Day 7, did not change between Days 7 and 14, and decreased significantly by 30 days at pasture (Day 44). The ΔPpl_{max} was decreased by Day 3, then remained unchanged to Day 14, and decreased significantly again by 30 days at pasture (Day 44).

Cytology of BALF was significantly affected by time and there were significant time/treatment interactions (Figs 5 and 6; Table 1). Total cell numbers in BALF were greatest at baseline (Day 1) and least after 30 days at pasture (Day 44). With

TABLE 2: Effect of atropine on lung function

	Day	Pre-atropine	Post atropine	n
$\Delta P_{pl_{max}}$ (cmH ₂ O)	7	20.9 ± 2.7	11.9 ± 1.5	11
	14	22.2 ± 3.6	10.7 ± 1.1	10
Pulmonary resistance (cmH ₂ O/l/s)	7	2.1 ± 0.3	1.4 ± 0.4	11
	14	1.7 ± 0.2	1.1 ± 0.1	10
Dynamic elastance (cmH ₂ O/l)	7	2.0 ± 0.2	1.1 ± 0.1	11
	14	2.0 ± 0.4	1.2 ± 0.1	10

Data are mean ± s.e. There was a significant effect of atropine on all measures of lung function on both Days 7 and 14. Because there was no effect of prednisone on the response to atropine, data from prednisone and no steroid treatments were combined. The effect of atropine was significant on all measurements at Days 7 and 14.

environmental management alone, total cell numbers did not decrease significantly until the horses had been at pasture for 30 days (Day 44). When prednisone was added, total cell numbers decreased significantly by Day 3, tended to increase again by Day 7, and decreased again after 30 days at pasture (Day 44). The changes in total cell numbers were largely due to changes in neutrophil numbers. In the absence of prednisone, neutrophil numbers did not decrease significantly until Day 14 and decreased further after 30 days at pasture (Day 44). With prednisone treatment, neutrophil numbers were significantly reduced by Day 3, remained level to Day 14 and decreased significantly again at pasture. Total lymphocytes tended to increase by Day 3 ($P < 0.076$) and were significantly increased at Days 14 and at pasture. The only significant change in total macrophages was a decrease between Days 3 and 7 in the absence of prednisone.

Changes in absolute cell numbers were reflected in the differential cell count of BALF (Table 1). With environmental management alone, the percent neutrophils decreased significantly by Day 3, remained constant through Day 14, and decreased significantly again at pasture. Addition of prednisone transiently decreased the neutrophil percentage by Day 3 to a value that was not different from that at pasture. The neutrophil percent tended to increase again at Days 7 and 14 and then decreased significantly again at pasture. The percent lymphocytes was significantly increased by Day 3 in both treatments. The percent macrophages increased by Day 3 in the prednisone treatment group, but not until Day 14 with environmental management alone.

The response to atropine was determined in 11 horses. The twelfth horse became very excited following atropine administration and it was not possible to measure lung function. On Day 7, administration of atropine resulted in a significant improvement in lung function: R_L , E_{dyn} , and $\Delta P_{pl_{max}}$ all decreased (Table 2). Neither the lung function prior to atropine nor the response to atropine was affected by prednisone treatment. On Day 14, lung function improved in 10 of the 11 horses after atropine administration. During the environment plus prednisone treatment, one horse developed a transient but very severe obstruction after atropine administration. The obstruction disappeared after the horse coughed and we therefore assumed it was due to release of a large mass of

secretions. This horse was treated as an outlier and statistics were run on the remaining horses. In the latter animals, atropine significantly improved lung function (Table 2).

Discussion

This study has confirmed that improvement in pulmonary function of RAO-affected horses can be achieved solely through environmental modification. This clinical observation has been reported at least since the mid-17th century (Markham 1656). In more recent times, our laboratory (Derksen *et al.* 1985) and others (Tesarowski *et al.* 1996) have demonstrated repeatedly the improvement in lung function and the resolution of airway inflammation that occurs when RAO-affected horses and ponies are taken from the stable to pasture. Others have demonstrated that rigorous stable hygiene will also cause improvement. Thomson and McPherson (1984) showed that 20 COPD-affected horses bedded on shredded paper, fed a complete cubed diet, and maintained in a stable that was washed regularly to minimise dust levels became asymptomatic in 8.4 ± 4.8 days (mean ± s.d.). In a more recent study, COPD-susceptible horses were maintained in clinical remission in a well-ventilated stable for 6 weeks while being fed grass silage and bedded on either wood shavings or good quality straw (Vandenput *et al.* 1998a, b).

Rigorous changes in feeding and bedding practices in a whole stable often are not possible and for that reason, we decided to test the efficacy of simply improving the management in a single stall. We demonstrated that feeding a pelleted diet and bedding the RAO-affected horse on shavings, while continuing to feed hay and bed on straw in the adjacent stalls, was sufficient to improve lung function within 3 days. Although an improvement in lung function occurred while the horses were stabled, further resolution of airway obstruction came about during the subsequent 30 days at pasture. This observation confirms that horses with RAO can have varying degrees of airway obstruction depending on the conditions in which they are housed. Exposure of horses to a dusty and mould-rich environment, by feeding them mouldy hay and bedding on straw, induces severe airway obstruction. Reduction of the dust levels by feeding pellets or silage and bedding on shavings or paper reduces the degree of airway obstruction but these animals still have some airway inflammation and obstruction. Keeping RAO-susceptible horses at pasture is optimal. It resolves airway inflammation and leads to the best airway function (Vandeput *et al.* 1998a, b; Votion *et al.* 1999).

Administration of atropine to our horses after 7 and 14 days in the improved environment showed that the residual airway obstruction was in large part due to bronchospasm. In RAO-affected horses, this bronchospasm is in part due to the actions of inflammatory mediators that facilitate cholinergically mediated smooth muscle contractions by actions on both parasympathetic nerves and smooth muscle itself (Olszewski *et al.* 1999). Atropine, a cholinergic antagonist, relaxes airway smooth muscle by blocking the M_3 -receptor that is activated by acetylcholine released from parasympathetic nerves.

Corticosteroids are employed commonly to treat horses with RAO. It is hoped that they will decrease inflammation within the airways and improve pulmonary function (Rush *et al.* 1998a, b). Dexamethasone and prednisone are the most commonly utilised systemic corticosteroids, with many practitioners selecting prednisone because of a perceived reduced risk of laminitis. Even though prednisone is widely prescribed for the treatment of RAO,

proof of its therapeutic effectiveness does not exist in the veterinary literature. The present study utilised an accepted anti-inflammatory dose of oral prednisone over a 14 day treatment course in order to determine if it would provide a synergistic benefit along with environmental modification. With regard to the resolution of airway obstruction, there was no benefit to the use of prednisone under the present experimental conditions. This does not mean, however, that prednisone would not have benefit in situations where environmental modification is not possible.

As has been reported numerous times, airway obstruction in RAO-affected horses was associated with neutrophilic inflammation of the airways (see Robinson *et al.* 1996 for review). Before the initiation of treatment, neutrophils comprised almost 80 percent of cells recovered by BALF. With environmental modification alone, total cell numbers in BALF did not decrease while the horses were stabled, and total neutrophil numbers did not decrease until Day 14. Over this period and, especially between Days 1 and 3, neutrophil total numbers did not change significantly, yet there was a considerable improvement in airway function as judged by E_{dyn} , R_L , and ΔPpl_{max} . This latter observation of a dissociation of airway function from neutrophil numbers suggests that neutrophils may not play a direct role in the initiation of airway obstruction. This same conclusion was suggested recently by Olszewski *et al.* (1999), who reported that mast-cell-derived mediators, rather than neutrophil products, facilitate cholinergically mediated bronchospasm in horses.

One might argue that prednisone lacked an effect on lung function because it was not absorbed from the intestinal tract. However, examination of the data on cell numbers in BALF refutes that possibility. On Day 3 of the study, prednisone treatment was associated with a significant reduction in total cell numbers as a result of a decrease in neutrophil numbers. Presumably, treatment with prednisone decreased the production of one or more of the neutrophil chemotactic factors being produced in the airways. Prednisone is known to inhibit the production of leukotriene B_4 by macrophages (Sebaldt *et al.* 1990; Wenzel *et al.* 1994; Dworski *et al.* 1994) and corticosteroids inhibit the production of interleukin-8 by airway epithelial cells (Marini *et al.* 1992; Kwon *et al.* 1994). Leukotriene B_4 is a potent neutrophil chemoattractant in horse lungs (Marr *et al.* 1998) and levels of interleukin-8 are increased in horses with RAO (Lavoie *et al.* 1999). Despite this anti-inflammatory effect of prednisone, there was no relief of airway obstruction. Once again, airway function did not follow neutrophil numbers.

The results of this study allow us to reach several important clinical conclusions. First, improving the environment in a single stall, by bedding on wood shavings and feeding a complete pelleted diet, is worthwhile. This management resulted in an improvement in lung function in RAO-affected horses within 3 days. Improvement in lung function required only modification of the immediate environment, not that of the entire stable. Second, addition of oral prednisone provided no additional benefit over environmental modification alone. Third, despite the relief of airway obstruction afforded by improving the stall environment, there was still considerable airway obstruction by bronchospasm at Days 7 and 14. It would therefore be useful to use a bronchodilator for horses in this situation. Finally, there is no substitute for pasture in the treatment of RAO. Airway function was best and inflammation least when horses had been at pasture for 30 days.

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Manufacturers' addresses

- ¹Purina Mills, St. Louis, Missouri, USA.
- ²Pharmacia Upjohn, Kalamazoo, Michigan, USA.
- ³Validyne, Northridge, California, USA.
- ⁴OEM Medical, Richmond, Virginia, USA.
- ⁵Buxco Electronics, Inc., Sharon, Connecticut, USA.
- ⁶Bivona, Gary, Indiana, USA.
- ⁷Life Technologies, Grand Island, New York, USA.
- ⁸Sigma Chemical Co., St. Louis, Missouri, USA.

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