# Effects of pentoxifylline on pulmonary function and results of cytologic examination of bronchoalveolar lavage fluid in horses with recurrent airway obstruction

Renaud Léguillette, DMV, MSc; Cyril Désévaux, DMV, MSc; Jean-Pierre Lavoie, DMV

**Objectives**—To determine the effects of pentoxifylline (PTX) administration on lung function and results of cytologic examination of bronchoalveolar lavage fluid in horses affected by recurrent airway obstruction (RAO).

**Animals**—10 RAO-affected horses.

**Procedures**—6 horses were orally administered PTX (16 g) mixed with corn syrup, and 4 horses were administered corn syrup alone, twice daily for 14 days. Pulmonary function was evaluated before administration (day 0) and on days 8 and 15. Bronchoalveolar lavage (BAL) was performed on days 0 and 15. Reversibility of airway obstruction was assessed by measuring pulmonary function before and after administration of atropine (0.02 mg/kg, IV). Serum concentration of PTX was measured in 4 horses 30 minutes and 2 and 4 hours after administration of PTX on days 1, 2, 3, 7, and 14.

**Results**—Administration of PTX to RAO-affected horses resulted in a decrease in elastance value on day 8 and on elastance and resistance ($R_L$) values on days 8 and 15. Results for cytologic examination of BAL fluid obtained on day 15 did not differ significantly, compared with values for day 0. Values of $R_L$ decreased in all horses following administration of atropine. When mixed in corn syrup and administered orally, PTX was poorly absorbed in horses, and there was noticeable variation in serum PTX concentrations over time and among horses.

**Conclusions and Clinical Relevance**—Based on these results, it can be concluded that administration of PTX at high doses improved respiratory function of RAO-affected horses maintained in an unfavorable environment. (*Am J Vet Res* 2002;63:459–463)

**Recurrent airway obstruction (RAO)** is a respiratory condition of horses that is characterized by bronchospasm, peribronchial cell infiltration, and accumulation of a predominantly neutrophilic exudate in the lumen of the small airways.[1] Inflammation of the small airways in horses with RAO results from inhalation of airborne particles (mainly molds and fungi); therefore, control of environmental dust is paramount to the treatment of horses with RAO.[1] Because of their potent anti-inflammatory properties, corticosteroids are commonly administered to affected horses. Prolonged parenteral administration of corticosteroids usually is avoided because of the severe adverse effects that can be observed with their usage.[2]

Cyclic nucleotides cAMP and cGMP play an important role in the regulation of smooth muscle tone of the airways and activation of inflammatory cells. Intracellular concentrations of these nucleotides are tightly regulated by **phosphodiesterases (PDE)**; thus, chemical alteration of PDE could potentially be used to control inflammation of the airways and bronchoconstriction of the smooth muscles seen in horses with RAO.

**Pentoxifylline (PTX)** is a methylxanthine derivative that is a nonselective inhibitor of PDE.[3] Pentoxifylline is a more potent inhibitor of contraction of human bronchi, compared with theophylline,[3] another nonselective PDE inhibitor. Theophylline has been used in horses with RAO because of its bronchodilating properties.[4] In addition to bronchodilation, PTX has potent anti-inflammatory and immunomodulatory properties.[5-13] Of particular interest for the treatment of horses with RAO, PTX inhibits the activation of neutrophils induced by proinflammatory cytokines, decreases the production of superoxide radicals by neutrophils, and reduces granular release of enzymes by neutrophils.[14-16] The combined bronchodilatory and anti-inflammatory properties of PTX led us to postulate that PTX administration to RAO-affected horses could improve their pulmonary function as well as reduce their pulmonary inflammation.

## Materials and Methods

**Horses**—Ten horses with RAO (9 mares and 1 gelding) that weighed between 390 and 498 kg (mean ± SEM, 444 ± 54 kg) were included in the study. Horses comprised 2 Quarter Horses, 1 Arabian, 4 Standardbreds, and 3 mixed-breed horses. Recurrent airway obstruction was diagnosed in all horses on the basis of medical history, clinical findings during physical examinations, and results of pulmonary function tests and cytologic examination of fluid obtained during **bronchoalveolar lavage (BAL)**. Criteria for inclusion were a history of chronic recurrent coughing, **maximal changes in transpulmonary pressure($\Delta P_L$)** > 15cm $H_2O$, > 10% neutrophils in BAL fluid, and results for CBC and serum biochemical analyses within the reference ranges. Endoscopy of the pharynx and trachea was performed to exclude obstructive abnormalities. None of the horses had received treatments for RAO during the 3 months preceding the study.

Received Aug 21, 2000.
Accepted Oct 24, 2000.
From the Département des Sciences Cliniques, Faculté de Médecine Vétérinaire, Université de Montréal, CP 5000, St-Hyacinthe, J2S2M2, QC, Canada (Léguillette, Lavoie); and the Faculté de Pharmacie, Université de Montréal, CP 6128, Montréal, H3C3J7, QC, Canada (Désévaux).
Supported by the Groupe de Recherche en Médecine Équine du Québec, Le Fonds du Centenaire; Université de Montréal; and Merial Canada Inc.
The authors thank Dr. Jérome Del Castillo and François Rousseau for technical assistance.
Address correspondence to Dr. Lavoie.

Horses were housed in the same barn for at least 1 month before and during the study. They were fed maintenance amounts of hay and grain and were bedded on straw. Management of the horses remained the same throughout the study. The study was approved by the Animal Welfare Committee of the University of Montreal.

**Collection and analysis of BAL fluid**—Bronchoalveolar lavage was performed as described elsewhere.[17] Briefly, horses were administered xylazine hydrochloride[a] (0.3 to 0.5 mg/kg, IV) and butorphanol tartrate[b] (10 mg, IV). A fiberoptic endoscope (190 cm in length, 14 mm in diameter) was inserted in the left nostril and progressively passed until its tip was wedged against the wall of a bronchus in the left lung. During insertion of the endoscope through the airways, several small boluses of a 0.5% solution of lidocaine hydrochloride[c] were administered to desensitize the bronchial mucosa, but only a small amount of lidocaine reached the portion of the lung that was lavaged. Two boluses (250 ml/bolus) of sterile isotonic saline (0.9% NaCl) solution were rapidly instilled in the bronchus and then immediately aspirated via the endoscope biopsy channel by use of a suction pump. Lavage fluid was recovered into a siliconized glass vessel and kept on ice until analysis, which was performed within 1 hour after sample collection.

Total nucleated cells in BAL fluid were counted by using a hemacytometer. Slides were prepared by use of 100 µl of BAL fluid, which was centrifuged (90 × g for 5 minutes); supernatant was decanted, and the pellet was spread on a slide and stained with modified Wright stain. A differential count was performed on at least 400 cells; epithelial cells were not included in the differential count.

**Pulmonary function tests**—Pulmonary function tests were performed as described elsewhere.[17] **Flow rate ($\dot{V}$)** was obtained by use of a heated pneumotachograph[d] and associated differential pressure transducer[e] that was fitted to a mask placed and sealed over the nose of each horse. Electronic integration of the flow signal provided **tidal volume ($V_T$)**. For each experiment, the system was calibrated by forcing air at known flow rates (between 0 and 10 L/s) through the pneumotachograph by use of a blower-rotameter equipment. **Transpulmonary pressure ($P_L$)** was obtained by use of a differential pressure transducer[f] by subtracting esophageal pressure from mask pressure. Esophageal pressure was measured with a balloon sealed over the end of a polyethylene catheter (inside diameter, 4.8 mm; outside diameter, 7.9 mm) placed in the distal third of the esophagus and distended with 3 ml of air. Distance between the nares and distal third of the esophagus was visually approximated and marked on the esophageal balloon catheter. Pressure tracings were monitored, and position of the esophageal balloon catheter was modified, if necessary, to obtain the maximalchanges in PL during a respiratory cycle ($\Delta P_L$) and to eliminate cardiac artifacts. Length of the inserted tubing was recorded for each horse, and the same length was always used in each horse during subsequent measurements. The pressure transducer was calibrated by use of a water manometer. Signals from the transducers were amplified and passed through a digital-analogue converter to a computer equipped with a program for data acquisition[g] and analysis.[h] The program provided values of $V_T$, minute expiratory ventilation, respiratory rate, expiratory and inspiratory times, and $\Delta P_L$ for each breath. Values of **pulmonary resistance ($R_L$)** and **pulmonary elastance ($E_L$)** were obtained by use of the following multiple regression equation for a single-compartment model of the lungs:

$$P_L = (E_L \times V) + (R_L \times \dot{V}) + K$$

where V is the volume, and K is the transpulmonary end-expiratory pressure. The coefficient of determination for the fit of the equation was calculated for each breath. Signals were sampled at a frequency of 120 Hz for 100 seconds, and all valid breaths were used for analysis.

**Experimental procedure**—Horses were randomly assigned to 2 groups. Six horses were orally administered PTX suspension by using 16 g of PTX[i] homogenized in corn syrup (volume for administration, 100 ml). The remaining 4 horses (control horses) were orally administered 100 ml of corn syrup. Treatments were administered twice daily at 8 AM and 8 PM for 14 days; horses were fed daily at 8:30 AM and 4:30 PM.

Pulmonary function measurements and BAL were performed prior to initial drug administration (day 0) and on day 15. Pulmonary function also was determined on day 8. Pulmonary function testing preceded BAL when both procedures were conducted on the same day. The reversibility of airway obstruction was determined by pulmonary function testing performed 20 minutes after the administration of atropine[j] (0.020 mg/kg, IV) 4 to 6 weeks after the last day of treatment.

Blood samples were collected 30 minutes and 2 and 4 hours after treatment on days 1, 2, 3, 7, and 14 from 4 horses administered PTX. Blood samples were collected into evacuated collection tubes[k] and allowed to clot. Tubes then were centrifuged, and serum was aspirated and stored frozen at –40 C within 3 hours after collection. Serum concentration of PTX was evaluated by use of high-performance liquid chromatography. Concentrations of PTX measured in serum samples obtained on a single day were averaged and adjusted on the basis of the body weight of each horse.

**Statistical analysis**—Differences between groups for selected pulmonary function tests and BAL variables on day 0 were evaluated by use of a Mann-Whitney test. Results of pulmonary function tests and cytologic examination of BAL fluid for each time period were compared by use of a Wilcoxon signed-rank test. Results of pulmonary function tests before and after atropine administration, on day 15, and after the atropine response test were compared by use of a Wilcoxon signed-rank test. For all tests, a value of $P < 0.05$ was considered significant.

Table 1—Mean ± SEM values of selected variables of pulmonary function in horses affected with recurrent airway obstruction before and after oral administration of 16 g of pentoxifylline to 6 horses or oral administration of corn syrup to 4 horses (control horses) twice daily for 14 days

| | Day | | |
|---|---|---|---|
| **Variable** | **0** | **8** | **15** |
| Pentoxifylline | | | |
| $\Delta P_L$ (cm $H_2O$) | 43.7 ± 4.6 | 24.9 ± 1.3* | 18.9 ± 1.6*† |
| $R_L$ (cm $H_2O$/L/s) | 2.85 ± 0.34 | 2.16 ± 0.37 | 1.61 ± 0.18*† |
| $E_L$ (cm $H_2O$/L) | 5.74 ± 1.57 | 2.09 ± 0.36* | 1.79 ± 0.33* |
| f (breaths/min) | 23.7 ± 5.4 | 19.2 ± 4.0 | 19.7 ± 3.6 |
| $V_T$ (L) | 5.1 ± 0.8 | 5.9 ± 0.9 | 5.2 ± 0.5 |
| $T_E$:$T_I$ | 1.50 ± 0.11 | 1.22 ± 0.06 | 1.28 ± 0.06 |
| Control | | | |
| $\Delta P_L$ (cm $H_2O$) | 36.3 ± 10.6 | 40.4 ± 8.7 | 39.3 ± 12.6 |
| $R_L$ (cm $H_2O$/L/s) | 2.48 ± 0.36 | 2.80 ± 0.24 | 2.67 ± 0.58 |
| $E_L$ (cm $H_2O$/L) | 3.29 ± 1.00 | 3.67 ± 0.93 | 3.21 ± 0.94 |
| f (breaths/min) | 18.0 ± 2.3 | 16.7 ± 2.2 | 16.6 ± 2.3 |
| $V_T$ (L) | 5.3 ± 0.1 | 5.6 ± 0.4 | 5.7 ± 0.4 |
| $T_E$:$T_I$ | 1.29 ± 0.09 | 1.51 ± 0.15 | 1.39 ± 0.13 |

*Within a row, value differs significantly ($P < 0.05$) from value for day 0.
†Within a row, value differs significantly ($P < 0.05$) from value for day 8.
Day 0 = First day of oral administration. $\Delta P_L$ = Maximal change in transpulmonary pressure. $R_L$ = Pulmonary resistance. $E_L$ = Pulmonary elastance. f = Respiratory rate. $V_T$ = Tidal volume. $T_E$:$T_I$ = Expiratory time-to-inspiratory time ratio.

## Results

Horses from both groups had a similar degree of airway obstruction and inflammation on day 0, as indicated by a lack of significant differences between the groups for $\Delta P_L$, $R_L$, $E_L$, respiratory rate, and the expiratory time-to-inspiratory time ratio (**Table 1**) as well as for total and differential cell counts of BAL fluid (**Table 2**). In contrast to control horses, PTX-treated horses had improved airway function, as indicated by significant decreases in $\Delta P_L$ and $E_L$ in the PTX-treated group on day 8 and in $\Delta P_L$, $E_L$, and $R_L$ on day 15 (**Fig 1 and 2**). Lung function in horses treated with PTX continued to improve during the second week of treatment, as indicated by a significant reduction in $\Delta P_L$ and $R_L$ between days 8 and 15. There was not a significant change in results of cytologic examination of BAL fluid in either group (Table 2). Values of $R_L$ decreased in 9 of 9 horses following administration of atropine, indicating that the airway obstruction was reversible.

Administration of PTX was tolerated well by all 6 horses, and adverse effects were not detected during the study. There was a noticeable variation in serum concentration of PTX over time and among horses (**Fig 3**). Mean ± SEM serum concentration of PTX 0.5 hours after administration was 2.82 ± 0.12 µg/ml. Mean daily

Table 2—Mean ± SEM values of selected variables for bronchoalveolar lavage fluid obtained from horses affected with recurrent airway obstruction before and after oral administration of 16 g of pentoxifylline to 6 horses or oral administration of corn syrup to 4 horses (control horses) twice daily for 14 days

| | Day | |
|---|---|---|
| **Variable** | **0** | **15** |
| Pentoxifylline | | |
| Fluid volume (ml) | 145 ± 18 | 151 ± 11 |
| Nucleated cells (× $10^9$/L) | 0.13 ± 0.04 | 0.29 ± 0.11 |
| Neutrophils (%) | 54.8 ± 13.23 | 42.0 ± 11.99 |
| Lymphocytes (%) | 21.62 ± 8.02 | 21.33 ± 4.92 |
| Macrophages (%) | 23.54 ± 8.04 | 36.04 ± 7.93 |
| Eosinophils (%) | 0.25 ± 0.19 | 1.25 ± 0.25 |
| Control | | |
| Fluid volume (ml) | 160 ± 24 | 142 ± 12 |
| Nucleated cells (× $10^9$/L) | 0.29 ± 0.14 | 0.13 ± 0.04 |
| Neutrophils (%) | 58.5 ± 16.31 | 45.8 ± 13.20 |
| Lymphocytes (%) | 15.49 ± 11.70 | 20.69 ± 8.74 |
| Macrophages (%) | 25.62 ± 8.50 | 31.94 ± 11.39 |
| Eosinophils (%) | 0.62 ± 0.37 | 1.42 ± 0.30 |

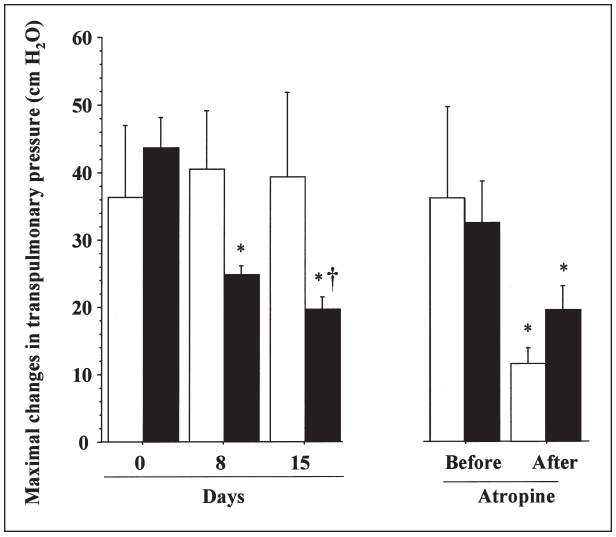


Figure 1—Mean ± SEM maximal changes in transpulmonary pressure in horses affected with recurrent airway obstruction (RAO) before and after oral administration of 16 g of pentoxifylline (PTX) to 6 horses (black bar) or oral administration of corn syrup to 4 horses (control horses, white bar) twice daily for 14 days (left panel). Four to 6 weeks after end of PTX administration, maximal change in transpulmonary pressure also was measured before and after administration of atropine (0.02 mg/kg, IV) in 5 RAO-affected PTX-treated horses and 4 RAO-affected untreated horses (right panel). *Value differs significantly ($P < 0.05$) from value for day 0. †Value differs significantly ($P < 0.05$) from value recorded on day 8. Day 0 = First day of oral administration.

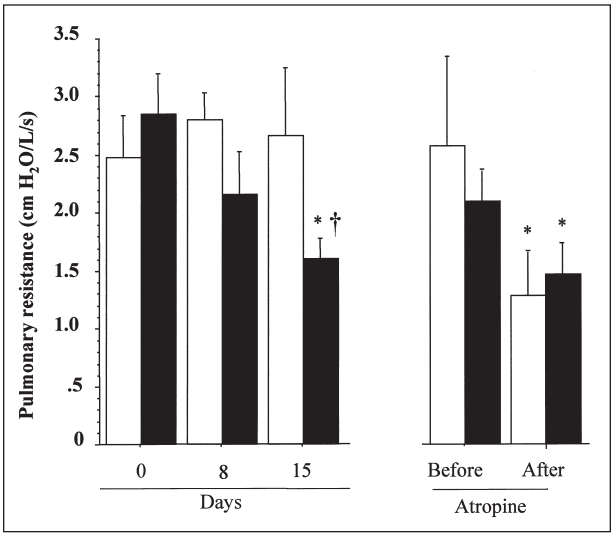


Figure 2—Mean ± SEM changes in pulmonary resistance before and after oral administration of PTX to 6 RAO-affected horses and oral administration of corn syrup to 4 RAO-affected horses (control group) twice daily for 14 days (left panel). Four to 6 weeks after end of PTX administration, pulmonary resistance also was measured before and after administration of atropine (0.02 mg/kg, IV) in 5 RAO-affected PTX-treated horses and 4 RAO-affected untreated horses (right panel). *See* Figure 1 for key.

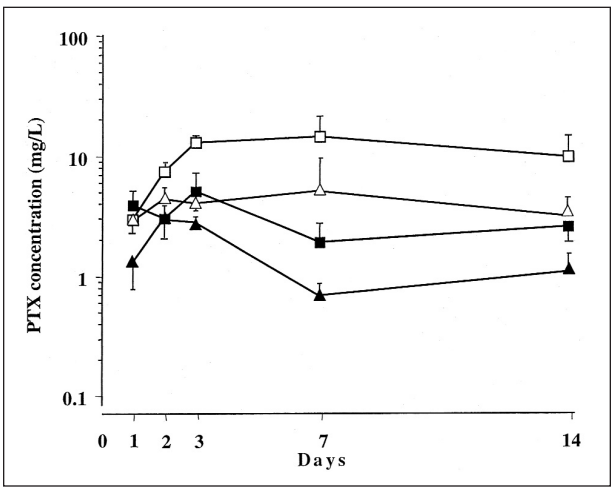


Figure 3—Mean ± SEM daily serum concentration of PTX measured in 4 RAO-affected horses that were orally administered 16 g of PTX mixed in corn syrup twice daily for 14 days. Values were corrected on the basis of body weight of each horse. Each symbol represents values for 1 horse. Day 0 = First day of oral administration.

serum concentrations of PTX increased markedly for the first 3 days of treatment in 3 horses.

## Discussion

Pentoxifylline is a nonspecific inhibitor of PDE that has numerous pharmaceutical properties.[12,13,18-20] Rheologic and anti-inflammatory effects of PTX have led to its use as a therapeutic agent for various diseases in horses, including navicular disease,[21] exercise-induced pulmonary hemorrhage,[21,22] and endotoxemia.[23-26] Pentoxifylline is approved in Canada for use in the treatment of horses with navicular disease.[l]

Pentoxifylline also has bronchodilatator properties.[3,27] In the study reported here, the degree of improvement in airway function of RAO-affected horses treated with PTX was of the same magnitude as that obtained with atropine, a potent bronchodilator in horses.[4,28] It has been reported[3] that PTX is a more potent inhibitor of contraction of the bronchi of humans, compared with the effects of theophylline, and that substantial bronchorelaxation can be obtained in vitro with PTX at concentrations as low as 1.4 µg/ml, a concentration achieved in most of the serum samples evaluated in our study (Fig 3). Airway function continued to improve during the second week of treatment with PTX, suggesting that additional improvement could possibly have resulted from a longer duration of treatment.

The dose of PTX evaluated in the study here was higher than those previously proposed for the treatment of diseases of horses.[24,26,29] It was selected on the basis that the oral absorption of PTX in horses is poor[29] and that high drug concentrations are required to achieve a substantial reduction in neutrophil activation.[30,31] The dose of PTX used in the study reported here was tolerated well by the horses, a finding that is in agreement with another study[32] in which investigators did not detect adverse effects when horses were administered 30 g of PTX daily for 6 weeks. Despite its poor absorption, the serum concentration of PTX measured in this study is similar to concentrations considered appropriate for the treatment of people with acute respiratory distress syndrome and asthma.[14,33,34] The minimal dose of PTX required for improvement of airway function in horses with RAO is not known, but it may be less than that used in this study, as suggested by the reversibility of airway obstruction in 1 horse that had a serum concentration of PTX < 3 µg/ml. It is possible that despite low serum concentrations of PTX, potent metabolites of PTX may have contributed to clinical efficacy, similar to the situation described in people.[31,33]

Lack of a reduction in neutrophilia in BAL fluid in the study reported here suggested that PTX did not have a measurable anti-inflammatory effect on the lung parenchyma. However, other studies[17,35,m,n] conducted by our laboratory group have revealed that cortico steroids, which are potent anti-inflammatory drugs devoid of direct bronchodilating properties, also may improve lung function of RAO-affected horses without a substantial reduction in pulmonary neutrophilia. This suggests that an anti-inflammatory effect of PTX cannot be completely ruled out in the horses reported here. The sequence of events that leads to inflammation of the small airways in RAO-affected horses is poorly defined, but arachidonate metabolites[36] and chemokines such as interleukin-8[37,o] and macrophage inhibitory peptide-2[37] may contribute to neutrophil chemotaxis and activation. Decrease in production of inflammatory mediators by PTX without inhibition of neutrophil chemotaxis could potentially attenuate pulmonary inflammation without reducing pulmonary neutrophilia. Support for this hypothesis is the fact that in some circumstances, PTX may enhance neutrophil migration and accumulation in lung tissues at concentrations sufficient to induce an anti-inflammatory effect.[38,39] The concentration of PTX required for inhibition of cytokine production in live horses is unknown, but PTX concentrations lower than those obtained in the study reported here have inhibited the production of proinflammatory cytokines in several in vitro equine models.[10,23]

Based on results of the study reported here, it can be concluded that the administration of PTX improves respiratory function of RAO-affected horses. Dose-titration studies would be required to determine the lowest dose required to achieve therapeutic effects in RAO-affected horses. Additional studies are necessary to determine whether the effects observed were solely the result of bronchodilation or were also attributable to a decrease in airway inflammation as a result of treatment with PTX.

[a]Rompun, Bayer Inc, Agriculture Division, Etobicoke, ON, Canada.
[b]Torbugesic, Ayerst Laboratories, Montreal, QC, Canada.
[c]Xylocard 1, Astra Pharma Inc, Missauga, ON, Canada.
[d]Fleisch No. 5, Oem Medical, Richmond, Va.
[e]Model 143PC03D microswitch, Honeywell, Scarborough, ON, Canada.
[f]Model HCXPM005D6V, Sensor Technics, Newport News, Va.
[g]Labdat 5.1, RHT Infodat, Montreal, QC, Canada.
[h]Anadat 5.1, RHT Infodat, Montreal, QC, Canada.
[i]Pentoxifylline, Laborio Chimico Internazionale, Milan, Italy.
[j]Atropine sulfate, MTC Pharmaceuticals, Cambridge, ON, Canada.
[k]Vacutainer tubes, Becton Dickinson and Co, Franklin Lakes, NJ.
[l]Navicon, Sterivet, Victoriaville, QC, Canada.
[m]Ammann VJ, Lavoie JP, Vrins AA. Effects of beclomethasone dipropionate in horses with chronic obstructive pulmonary disease (COPD) (abstr), in *Proceedings*. 13th Annu Med Forum Am Coll Vet Intern Med 1995;1037.
[n]Lavoie JP, Léguillette R, Charette L, et al. Comparison of dexamethasone and the LTD4 receptor antagonist L-708,738 in an equine COPD model (abstr). *Am J Respir Crit Care Med* 2000:158:A185.
[o]Lavoie JP, Maghni K, Desnoyer M, et al. Expression of cytokine messenger mRNA in bronchoalveolar cells of horses with heaves (abstr). *Am J Respir Crit Care Med* 1999;159:A510.

## References


1. Robinson NE, Derksen FJ, Olszewski MA, et al. The pathogenesis of chronic obstructive pulmonary disease of horses. *Br Vet J* 1995;152:283–306.
2. Lavoie JP. Chronic obstructive pulmonary disease. In: Robinson NE, ed. *Current therapy in equine medicine*. 4th ed. Philadelphia: WB Saunders Co, 1997;431–435.
3. Cortijo J, Bou J, Beleta J, et al. Investigation into the role of phosphodiesterase IV in bronchorelaxation, including studies with human bronchus. *Br J Pharmacol* 1993;108:562–568.
4. Pearson EG, Riebold TW. Comparison of bronchodilators in alleviating clinical signs in horses with chronic obstructive pulmonary disease. *J Am Vet Med Assoc* 1989;194:1287–1291.
5. Han J, Thompson P, Beutler B. Dexamethasone and pentox-

ifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signaling pathway. *J Exp Med* 1990; 172:391–394.

6. van Furth AM, Steenwijk TM, Langermans JA, et al. In vitro effect of dexamethasone, pentoxifylline, and anti-endotoxin monoclonal antibody on the release of proinflammatory mediators by human leukocytes stimulated with *Haemophilus influenzae* type B. *Pediatr Res* 1994;35:725–728.

7. van Furth AM, Seijmonsbergen EM, Langermans JA, et al. Effect of xanthine derivates and dexamethasone on *Streptococcus pneumoniae*-stimulated production of tumor necrosis factor alpha, interleukin-1 beta (IL-1 beta), and IL-10 by human leukocytes. *Clin Diagn Lab Immunol* 1995;2:689–692.

8. Chen YL, Le Vraux V, Giroud J, et al. Anti-tumor necrosis factor properties of non-peptide drugs in acute-phase responses. *Eur J Pharmacol* 1994;271:319–327.

9. Louie A, Baltch AL, Franke MA, et al. Comparative capacity of four antifungal agents to stimulate murine macrophages to produce tumor necrosis factor alpha: an effect that is attenuated by pentoxifylline, liposomal vesicles, and dexamethasone. *J Antimicrob Chemother* 1994;34:975–987.

10. Milam SB, Mackay RJ, Skelley LA. Secretion of tumor necrosis factor by endotoxin-treated equine mammary exudate macrophages: effect of dexamethasone and pentoxifylline. *Cornell Vet* 1992;82:435–446.

11. Boogaerts MA, Malbrain S, Meeus P, et al. In vitro modulation of normal and diseased human neutrophil function by pentoxifylline. *Blut* 1990;61:60–65.

12. Stellin GP, Waxman K. Current and potential effects of pentoxifylline. *Compr Ther* 1989;15:11–13.

13. Samlaska CP, Winfield EA. Pentoxifylline—clinical review. *J Am Acad Dermatol* 1994;30:603–621.

14. Neuner P, Klosner G, Schauer E, et al. Pentoxifylline in vivo down-regulates the release of IL-1 beta, IL-6, IL-8 and tumour necrosis factor-alpha by human peripheral blood mononuclear cells. *Immunology* 1994;83:262–267.

15. Oka Y, Murata A, Nishijima J, et al. Inhibitory effect of pentoxifylline and prostaglandin E1 on the release of neutrophil elastase from FMLP-stimulated neutrophils. *J Med* 1991;22:371–382.

16. Currie MS, Rao KM, Padmanabhan J, et al. Stimulus-specific effects of pentoxifylline on neutrophil CR3 expression, degranulation, and superoxide production. *J Leukoc Biol* 1990;47:244–250.

17. Lapointe JM, Lavoie JP, Vrins A. Effects of triamcinolone acetonide on pulmonary function and bronchoalveolar lavage cytologic features in horses with chronic obstructive pulmonary disease. *Am J Vet Res* 1993;54:1310–1316.

18. Hawkins ES, Ribeiro HA. Pentoxifylline review. *J Am Podiatr Med Assoc* 1987;77:645–647.

19. Zabel P, Entzian P, Dalhoff K, et al. Pentoxifylline in the treatment of sarcoidosis. *Am J Respir Crit Care Med* 1997;155:1665–1669.

20. Anaya JM, Espinoza LR. Phosphodiesterase inhibitor pentoxifylline: an antiinflammatory/immunomodulatory drug potentially useful in some rheumatic diseases. *J Rheumatol* 1995;22:595–599.

21. Weiss DJ, Evanson OA, Geor RJ. The effects of furosemide and pentoxifylline on the flow properties of equine erythrocytes: in vitro studies. *Vet Res Commun* 1994;18:373–381.

22. Geor RJ, Weiss DJ, Burris SM, et al. Effects of furosemide and pentoxifylline on blood flow properties in horses. *Am J Vet Res* 1992;53:2043–2049.

23. Barton MH, Moore JN. Pentoxifylline inhibits mediator synthesis in an equine in vitro whole blood model of endotoxemia. *Circ Shock* 1994;44:216–220.

24. Barton MH, Moore JN, Norton N. Effects of pentoxifylline infusion on response of horses to in vivo challenge exposure with endotoxin. *Am J Vet Res* 1997;58:1300–1307.

25. Barton MH, Ferguson D, Davis PJ, et al. The effects of pentoxifylline infusion on plasma 6-keto-prostaglandin F1 alpha and ex vivo endotoxin-induced tumour necrosis factor activity in horses. *J Vet Pharmacol Ther* 1997;20:487–492.

26. Baskett A, Barton MH, Norton N, et al. Effect of pentoxifylline, flunixin meglumine, and their combination on a model of endotoxemia in horses. *Am J Vet Res* 1997;58:1291–1299.

27. Nolte D. Pulmonary function tests on the bronchospasmolytic effect of 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine. *Arzneimittelforschung* 1971;21:1453–1456.

28. Jean D, Vrins A, Lavoie JP. Monthly, daily, and circadian variations of measurements of pulmonary mechanics in horses with chronic obstructive pulmonary disease. *Am J Vet Res* 1999;60:1341–1346.

29. Crisman MV, Wilcke JR, Correll LS, et al. Pharmacokinetic disposition of intravenous and oral pentoxifylline in horses. *J Vet Pharmacol Ther* 1993;16:23–31.

30. Weiss DJ, Geor RJ, Burris SM, et al. Effects of pentoxifylline on equine neutrophil function and flow properties. *Can J Vet Res* 1992;56:313–317.

31. Sullivan GW, Carper HT, Novick WJJ, et al. Inhibition of the inflammatory action of interleukin-1 and tumor necrosis factor (alpha) on neutrophil function by pentoxifylline. *Infect Immun* 1988; 56:1722–1729.

32. Essais pharmacologiques de la pentoxifylline chez le cheval. Victoriaville, QC, Canada: Rhone-Mérieux Canada, 1994;110–115.

33. Smith RV, Waller ES, Doluisio JT, et al. Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986;75:47–52.

34. Entzian P, Bitter-Suermann S, Burdon D, et al. Differences in the anti-inflammatory effects of theophylline and pentoxifylline: important for the development of asthma therapy? *Allergy* 1998; 53:749–754.

35. Grunig G, Hermann M, Howald B, et al. Partial divergence between airway inflammation and clinical signs in equine chronic pulmonary disease. *Equine Vet J* 1989;21:145–148.

36. Watson ED, Sweeney CR, Steensma KA. Arachidonate metabolites in bronchoalveolar lavage fluid from horses with and without COPD. *Equine Vet J* 1992;24:379–381.

37. Franchini M, Gilli U, Akens MK, et al. The role of neutrophil chemotactic cytokines in the pathogenesis of equine chronic obstructive pulmonary disease (COPD). *Vet Immunol Immunopathol* 1998;66:53–65.

38. Naureckas ET, Factor P, Benjaminov O, et al. Pentoxifylline does not protect against hyperoxic lung injury in rats. *Eur Respir J* 1994;7:1397–1402.

39. Elferink JG, Huizinga TW, de Koster BM. The effect of pentoxifylline on human neutrophil migration: a possible role for cyclic nucleotides. *Biochem Pharmacol* 1997;54:475–480.