Efficacy of Inhaled Levalbuterol Compared to Albuterol in Horses with Recurrent Airway Obstruction

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Background: The (R)-enantiomer of racemic albuterol (levalbuterol) has bronchodilatory properties whereas the (S)-enantiomer causes adverse effects in human airways, animal models, and isolated equine bronchi. Lavalbuterol is commercially available and improves pulmonary function of asthmatic patients with a longer duration of effect than albuterol. 

Objective: To determine the dose at which inhaled levartebrol produces maximal bronchodilatory effect (EDmax) and determine its duration of action in recurrent airway obstruction (RAO)-affected horses in comparison to racemic albuterol.

Animals: Nine horses with inducible and reversible RAO.

Methods: Randomized, crossover trial. Horses were challenged with moldy hay to induce airay obstruction. Horses were treated with nebulized albuterol or levartebrol chosen randomly. Pulmonary function testing (PFT) was measured before and for up to 3 hours after bronchodilatation challenge. Maximum change in transpulmonary pressure (DPmax) was measured to assess the dose effect and duration of action of each drug. After a 24 hours washout period, the bronchodilatation challenge was repeated with the second bronchodilator.

Results: The duration of effect was 60 minutes for albuterol and 120 minutes for levartebrol. The dose of bronchodilator EDmax was not significantly different between albuterol and levartebrol (EDmax = 125.0 [125–125 µg] and EDmax = 188 [125–188 µg] respectively, P = .068). The magnitude of bronchodilatation was not significantly different between the 2 treatments (61.1 and 59.9% decrease in DPmax for albuterol and levartebrol respectively, P = .86).

Conclusions and clinical importance: Levalbuterol is as effective a bronchodilator as albuterol; although levartebrol lasts twice as long as albuterol, its duration of action is still too short to make it practical for RAO treatment.

Key words: Aerosol treatment; Bronchodilator; Heaves.
bronchoconstriction in isolated equine bronchi in vitro, but, there is no report regarding the clinical effect of levalbuterol in horses. Levalbuterol is commonly used in human medicine because it improves pulmonary function and provides up to 6 hours of bronchodilatation. However, recent evidence has shown no clinical benefit of levalbuterol versus albuterol in adult patients with asthma and chronic obstructive pulmonary disease (COPD). The purpose of our study was to compare the bronchodilatory effect as well as the duration of action of levalbuterol and albuterol in horses with an acute episode of RAO.

Materials and Methods

Study Design

All methods were approved by the Purdue University Animal Care and Use Committee.

Nine horses (3 geldings, 6 mares; age range, 9–24 years) owned by Purdue University and with a history of inducible and reversible RAO were involved in this randomized, crossover trial. All of the horses remained on pasture on a complete pelleted feed for at least 2 months before the trial to achieve clinical remission. The animals were transported to the research facilities and resided there for the duration of the trial. On arrival, a physical examination and pulmonary function testing (PFT) were performed.

The horses were housed in individual stalls bedded with wood shavings and fed complete pellet feed as well as free choice hay placed in a hay net. In addition, they were exposed to moldy hay during 2 weeks of exposure. None of them developed anorexia or clinically relevant weight loss throughout the study. Results of baseline PFT measurements were repeated after switching treatment drug. Changes in PFT were compared between both drugs administered. Changes in PFT variables between baseline and subsequent time points were compared using Friedman ANOVA. Post-hoc tests were conducted using Wilcoxon matched pairs test when appropriate. Association between DP max at baseline and ED max was assessed by Spearman’s rank correlation. Data were summarized as median and interquartile range (IQR) and significance was defined as P < .05.

Results

All 9 horses met the inclusion criteria and responded to the moldy hay during 2 weeks of exposure. None of them developed anorexia or clinically relevant weight loss throughout the study. Results of baseline PFT (DP max, R l and C dyn) before administration of bronchodilators were not statistically different between the 2 treatment groups (P = .76).

The mean duration of bronchodilator effect was 60 minutes for albuterol and 120 minutes for levalbuterol (Fig 1). A comparable response was observed with R l data whereby albuterol effect lasted 40 minutes and levalbuterol effect was significant up to 120 minutes (Fig 2). Bronchodilator effect on C dyn followed a similar trend but was only statistically significant for 10–40 minutes. Two of the 9 horses continued to experience decreased DP max 3 hours after levalbuterol administration. The effects on PFT were noted after the first dose (63 µg) of either albuterol or levalbuterol and resulted in average decreases of 50 and 56% in DP max respectively. The calculated ED50% and ED max of the doses were not significantly different between albuterol (ED50% = 43.6 [38.2–47.3 µg] and ED max = 125.0 [125–125 µg]) and levalbuterol (ED50% = 39.7 [35.0–52.5 µg; P = .40] and ED max = 188 [125–188 µg; P = .068]; Fig 3). Similarly, the relative magnitude of bronchodilatation was not significantly different between the 2 treatments (61.1 [43.1–67.9] and 59.9 [52.2–63.6] % decrease in DP max for albuterol and levalbuterol respectively; P = .86). There was no significant correlation between DP max at baseline and ED max.

Pulmonary Function Test (PFT)

An esophageal balloon catheter was placed to obtain measurements analogous to pleural pressure. The position of the catheter was estimated by measuring the distance between the horse’s nostrils to mid thorax. The horse was placed in stocks with no sedation and an air-tight mask was fitted around the horse’s muzzle with the port of the mask holding the pneumotachometer to measure airflow. Esophageal pressure and airflow output signals from both devices were recorded simultaneously by computer software for 2 minutes to average the measurement of DP max and calculation of pulmonary R l and C dyn over 10 adequate breaths.

Bronchodilator Challenge

A first dose (62.5 µg) of albuterol sulfate or levalbuterol hydrochloride solution was chosen randomly by flipping a coin. This low dose corresponded to 0.15 mL of the bronchodilator solution as measured with a 1-mL syringe and given nondiluted. The bronchodilator was administered using an ultrasonic nebulizer and DP max measured 5 minutes later. The doses were repeated and the DP max was measured 5 minutes after each dose to evaluate the effects of cumulative bronchodilator administration and the dose at which maximal bronchodilatation was achieved. If the DP max reached a plateau consisting of a difference ≤30% between 2 successive doses, the air-tight mask was repositioned and PFT repeated 10, 20, 30, 40, 60, 90, 120, 180 minutes after the last dose of bronchodilator to determine the duration of the treatment effect, as previously described. After a washout period of 24 hours, physical examination and clinical scores were obtained to ensure that enrollment criteria were met again, and measurements were repeated after switching treatment drug.

The dose of bronchodilator that resulted in a 50% decrease in DP max (ED50%) was calculated by linear interpolation and the dose resulting in maximum bronchodilatation (ED max) was determined as the first dose of the plateau effect.
Levalbuterol, a β-agonist containing only the (R)-enantiomer of racemic albuterol, has been developed for human asthmatic patients to avoid the adverse effects of the (S)-enantiomer. To our knowledge, no previous studies have compared the use of levalbuterol and racemic albuterol for the treatment of horses with an acute episode of RAO.

Our results suggest that there are no significant differences in the magnitude of improvement in pulmonary function achieved by both bronchodilators, although the effects of levalbuterol lasted twice as long as those of albuterol (2 versus 1 hour respectively). No adverse effects were noted with this single short-term treatment with either bronchodilator, but future studies using daily treatment over several days would be needed to further assess this possibility. Despite this longer duration of action, the return of pulmonary pressures to baseline values by 180 minutes limits the use of levalbuterol to a rescue medication for horses with an acute RAO crisis or as a diagnostic method to confirm reversibility of airway obstruction.

Before the bronchodilator challenge, there was no significant difference in pulmonary function (DP\textsubscript{max}, R\textsubscript{L}, and C\textsubscript{dyn}) between each arm of the study, demonstrating that a washout period of 24 hours was adequate, as previously reported.

The average albuterol dose that induced a maximum bronchodilatory effect (125 μg) is markedly lower than...
the dose reported in previous studies (360–540 µg).4,5 This difference suggests that a higher proportion of drug was deposited in the lung using the ultrasonic nebulizer, presumably because of the smaller particle size delivered with the nebulizer compared to the hand-held device used in the previous studies.4 The nebulizer was easy to place and it took approximately 1 minute to administer each dose. The horses showed no adverse behavior throughout the bronchodilator challenge, similar to reports in previous studies.18 Bronchodilatation was significant after the first dose (63 µg) of either albuterol or levalbuterol, which corresponded to 0.15 mL of solution. We did not attempt to start the bronchodilator challenge with a lower dose because of the difficulty in accurate measurement of small volumes.

The deposition of the aerosol reaching the lungs in horses with ultrasonic nebulizers (5.09 ± 0.66%) is lower than the average 10% of aerosol deposition achieved in human patients.18 This difference is likely attributed to horses being nasal breathers, causing higher filtration. In addition, the deposition of small-sized aerosol particles in the human lung is augmented by deep inhalation, followed by a period of breath-holding at total lung capacity. This maneuver is not possible in horses.19-21 Horses experiencing an acute RAO episode tend to have rapid and shallow breaths that would be expected to decrease lung deposition of the bronchodilator. However, the doses of albuterol and levalbuterol resulting in EDmax in horses (125 and 188 µg, respectively) were very small compared to EDmax reported in human patients with severe asthma exacerbation (7.5 and 3.25 mg respectively).22 An additional effect from oral absorption of drugs deposited in the nasopharynx is unlikely because it would be expected to result in a delayed therapeutic effect, but this phenomenon was not observed in our study. Furthermore, there is evidence that oral albuterol is poorly absorbed in the horse21 and a closely related compound, terbutaline, also is not bioavailable orally in horses.23 Therefore, nebulized albuterol and levalbuterol are highly potent bronchodilators in horses with acute RAO exacerbation.

The effect of levalbuterol lasted 2 hours in RAO horses compared to 6 hours in human asthmatic patients.12,24 This decreased duration of action of levalbuterol in the horse is similar to that observed with another bronchodilator, salmeterol xinafoate.25 Salmeterol in human asthmatic patients has a duration of action of 12 hours and only 6 hours in horses with RAO. We hypothesized that the difference might be attributed to rapid drug clearance from the lung because of enhanced alveolar and bronchial absorption secondary to increased airway epithelial permeability25 or a species-specific pharmacokinetic difference in disposition of the drug. There are no validated explanations of why the duration of action of these bronchodilators is shorter in horses than in people.

Our results suggest that levalbuterol is effective to treat acute RAO in horses but, the only benefit of levalbuterol is the slightly longer duration of bronchodilatory effect compared to albuterol. There was no statistically significant difference in PFT after EDmax using either bronchodilator. These results suggest that both bronchodilators achieve a similar degree of bronchodilatation in horses, as opposed to humans in whom levalbuterol is more efficient at improving pulmonary function in addition to having a longer acting bronchodilatory effect than albuterol.5

In conclusion, unlike findings in human asthmatic patients, administration of levalbuterol to horses with RAO did not result in greater bronchodilatation compared to albuterol. Levalbuterol is an effective bronchodilator, but the short duration of action makes this drug nonpractical for treatment of RAO.

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Footnotes

a Tygon lab catheter, ¾ “ID x 3/8” OD, Cole Parmer, Vernon Hills, IL
b Equine AeroMask, Trudell Medical International, London, Ontario, Canada
c No. 4 Fleisch, EMKA Technologies, Paris, France
d Pulmonary mechanics analyzer, XA version, Buxco Electronics Inc, Sharon, CT
e 1.25 mg of albuterol sulfate in 3-mL unit-dose vial, Nephron Pharmaceuticals Corporation, Orlando, FL
f Xopenex®, 1.25 mg of levalbuterol in 3-mL unit-dose vial, Sunovion Pharmaceuticals Inc., Marlborough, MA

Acknowledgment

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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