Both an external nasal strip device (FLAIR™) and furosemide significantly attenuated pulmonary hemorrhage in Thoroughbred horses following a 2-minute bout of high-speed treadmill exercise. Given the purported ergogenic effects of furosemide and the general concerns associated with drug use in racehorses, the external nasal strip is a viable alternative for the attenuation of exercise-induced pulmonary hemorrhage. Authors’ addresses: Kentucky Equine Research, Inc., 3910 Delaney Ferry Road, Versailles, KY 40383 (Geor and Pagan); EquiGym Products, LLC, 278 Clintonville Rd., Paris, KY 40361 (Ommundson); CNS Inc., 7615 Smetana Lane, Minneapolis, MN 55439 (Fenton). © 2001 AAEP.

1. Introduction

In North American racing jurisdictions, the loop diuretic furosemide is administered to horses for prophylaxis of exercise-induced pulmonary hemorrhage (EIPH).1,2 Current evidence indicates that furosemide is administered to more than 70% of Thoroughbreds racing in the United States and Canada. However, whether furosemide is effective for prophylaxis of EIPH is controversial. Studies that have employed endoscopic examination of the trachea as a means for identifying horses with pulmonary hemorrhage have not detected an effect of furosemide on the incidence of EIPH in Thoroughbred racehorses.3,4 On the other hand, there is some evidence that the drug decreases the severity of pulmonary bleeding as assessed by the amount of blood in the trachea.5 Conversely, furosemide administration (250 mg intravenously [i.v.]) 4 hours before galloping did not have a detectable effect on the number of red blood cells (RBC) in samples of bronchoalveolar lavage (BAL) fluid obtained 45 minutes after exercise.6

Recently, an external nasal strip, designed to provide mechanical support to the rostral regions of the nasal passages and lessen inspiratory resistance, has been marketed for the prophylaxis of EIPH in horses. Preliminary studies have indicated that this device attenuates EIPH in horses undergoing near maximal treadmill exercise.6

The objective of the present study was to examine the effects of an external nasal strip, furosemide, and a combination of both treatments on pulmonary hemorrhage in horses during intense treadmill ex-
equivalent to 120% VO₂max was calculated for each horse. From linear regression analysis, an incremental exercise test performed 3 weeks before a standardized exercise test (SET), 2) a nasal strip (NS) trial in which a nasal strip (FLAIR™) was applied 5 minutes before the SET, and 4) a nasal strip and furosemide (NS + FR) trial in which horses received both treatments. During the SET in the FR and NS + FR trials, horses carried weight (a saddle) equal to the urinary and insensible weight losses that occurred over the 3.75 hours after furosemide administration. Trials in individual horses were performed at least 14 days apart.

The horses were 8 clinically normal Thoroughbreds (2 mares, 5 geldings, and 1 intact male; age, 3–10 years; weight, 470–555 kg). Five horses were in active race training, with all conditioning performed on a high-speed treadmill and a mechanical horse exerciser. One of these horses had a history of EIPH. Two horses had not raced for more than 2 years, and 1 horse was unraced; these horses were fully acclimated to running on the treadmill. All conditioning was performed 4–5 days per week for a minimum of 12 weeks preceding the study. The maximum rate of oxygen consumption (VO₂max) was measured during an incremental exercise test performed 3 weeks before the first SET. From linear regression analysis, the running speed that elicited an oxygen demand equivalent to 120% VO₂max was calculated for each horse.

On the day of each trial, between 0630 and 0830 hours, the horse was weighed, saline or furosemide was administered, and food and water was removed from the stall. The horse was weighed 3.75 hours after furosemide or saline administration. For the FR and NS + FR trials, a saddle and saddle pad was applied. The amount of weight added to the horses was calculated as the difference between initial body weight, recorded immediately before furosemide administration, and the body weight recorded 3.75 hours later, minus the weight of feces produced during the 3.75 hour period. Excessive tightening of the girth strap was avoided to minimize any effect of the saddle/girth on the mechanics of breathing during running. Five minutes before the NS and NS + FR trials, a nasal strip was applied according to the manufacturer’s directions. With treadmill set at a 3° incline, horses completed a 5 minute warm-up at 4 m/s followed by a 1 minute walk (1.6 m/s). The treadmill was then accelerated to a speed estimated to produce an oxygen demand of 120% VO₂max in each horse (14.2 ± 0.2 m/s). The transition from the walk to the target running speed was accomplished in 5–6 seconds. Horses ran at this speed for 2 minutes. After the sprint, horses completed a 15 minute cool down (10 minutes trotting and 5 minutes walking).

A. Bronchoalveolar Lavage

BAL samples were obtained one week before and after the incremental exercise test (2 weeks before the start of the experimental trials). These samples were used to determine the number of RBCs and other cell types in the BAL fluid in the absence of strenuous exercise. For the SET trials, BAL was performed 30 minutes after completion of the sprint. Horses were positioned in stocks and sedated with a combination of xylazine (0.5–0.7 mg/kg i.v.) and butorphanol (0.01 mg/kg i.v.). After 5 minutes, BAL was performed to quantitate the amount of EIPH, as previously described. A flexible BAL tube was passed through the right naris until it wedged in a subsegmental bronchus. A 0.05% lidocaine solution (20–40 ml) was used to desensitize the airways during passage of the BAL tube. Three hundred milliliters of lactated Ringers solution in 60 ml aliquots was infused. After 2–3 breaths, the fluid was aspirated into clean 60 ml syringes. Within 15 minutes of collection, the recovered fluid was centrifuged at 300 g for 10 minutes. The cell pellet was resuspended in phosphate buffered saline (pH = 7.4, 300 mOsm) and the RBCs were counted using an automated cell counter to determine the number of RBCs per milliliter of recovered fluid. Total white blood cell (WBC) count was also determined using an automated cell counter and for resting BAL samples, cytospin preparations were processed with a Wright’s stain for evaluation of differential cell counts, including the number of haemosiderophages.

B. Statistical Analysis

The data were analyzed using a one-way repeated measures analysis of variance (repeated measures on treatment). Because the data for RBC count in BAL fluid did not exhibit homogenous variance, these data were subject to logarithmic transformations prior to analysis of variance. Post-hoc analysis was performed using the Student-Newman-Keul test with a type I error rate of 5%. The data are presented as means ± SEM.

3. Results

VO₂max of the 8 horses was 153.3 ± 3.9 ml/kg per minute at a treadmill speed of 12.2 ± 0.2 m/s. Due to fatigue, one horse did not complete any of the sprint exercise tests; run times for this horse ranged between 90 and 100 seconds. One horse bled from the nostril during the C trial. Endoscopy confirmed the presence of blood in the trachea and lower airways.
A. Bodyweight

Combined urinary and insensible weight losses over the 3.75 hours after furosemide or saline administration were significantly (p < 0.001) greater in the FR (10.3 ± 0.8 kg) and NS + FR (10.0 ± 1.0 kg) trials than in the C (1.5 ± 0.4 kg) and NS (1.9 ± 0.4 kg) trials. However, after addition of weight to the horses in the FR (10.0 ± 0.2 kg) and NS + FR (9.7 ± 0.3 kg) trials, body weight during the SET did not differ among treatments (C, 505.1 ± 8.6 kg; NS, 509.3 ± 10.7 kg; FR, 505.6 ± 11.1 kg; NS + FR, 507.2 ± 10.7 kg).

B. Bronchoalveolar Lavage

Mean RBC and WBC counts and haemosiderophage percentage did not differ between the pre- and post-VO\textsubscript{2max} samples. For the exercise trials, fluid recovery during BAL ranged from 49 to 85% with a mean of 70 ± 3% (210 ± 15 ml). Recovery percentage did not differ between experimental conditions. There was a highly significant (p < 0.001) effect of treatment on RBC count in BAL fluid. In all horses, RBC count was highest in the C trial and ranged from 9.1 to 169.6 × 10\(^6\)/ml of BAL fluid, with a mean of 61.1 ± 33.9 × 10\(^6\)/ml. In all horses pulmonary hemorrhage was reduced in the NS, FR, and NS + FR trials relative to the C trial (Fig. 1). Mean RBC count was significantly lower in the NS + FR trial than in the NS trial, but treatments NS and FR were not significantly different. Overall, mean RBC count was decreased (p < 0.05) by 45.8 ± 12.1%, 66.1 ± 10.0%, and 67.8 ± 11.1% in the NS, FR, and NS + FR trials, respectively, compared with the C trial. There was no significant difference between treatments for BAL fluid WBC count (554 ± 99, 524 ± 131, 497 ± 186, and 591 ± 177 × 10\(^3\)/ml in C, NS, FR, and NS + FR, respectively).

4. Discussion

This study demonstrated that use of both an external nasal strip device and furosemide resulted in a significant decrease in the pulmonary hemorrhage associated with high-intensity exercise in horses. Because the RBC count in BAL fluid did not differ between the FR and NS + FR trials, there did not seem to be an advantage to the combined use of the external nasal strip and furosemide in the prophylaxis of EIPH. These results confirm the findings of an earlier investigation\(^6\) that also demonstrated a reduction in pulmonary hemorrhage with use of the nasal strip device.

BAL has been proposed as a useful method for semi-quantification of hemorrhage in the alveoli and small airways associated with exercise.\(^7\,\text{a}\) and post-exercise BAL has been used in studies that evaluated the efficacy of furosemide\(^5\) and the external nasal strip device\(^6\) for the prophylaxis of EIPH. Several points deserve emphasis in considering the use of this technique for the assessment of pulmonary hemorrhage in horses following strenuous exercise. First, imaging and postmortem studies have demonstrated that the dorsocaudal lung lobes are the primary site of hemorrhage in horses with EIPH.\(^9\) Second, radiographic studies have shown that a blindly passed BAL tube will consistently lodge in the dorsal caudal portion of the lung.\(^10\) Therefore, this technique does permit sampling of the area of the lung where bleeding occurs.

Compared with the control condition, the external nasal strip (NS trial) reduced the BAL RBC count by more than 40%. Similar to the previous study by Poole et al.,\(^6\) horses that demonstrated the greatest hemorrhage during the C trial also evidenced the most substantial reduction in EIPH in the NS trial. The mechanism for reduced EIPH with the external nasal strip has not been elucidated. Although stress failure of capillaries has been primarily attributed to pulmonary vascular hypertension,\(^11\) it has also been hypothesized that extravascular factors, particularly the highly negative intrapulmonary pressures during inspiration, contribute to the critical increase in capillary transmural pressure.\(^6\) It has been further proposed that dynamic restriction of the nasal airways during exercise may increase inspiratory resistance and contribute to the stress failure of pulmonary capillaries by induction of more negative intrapulmonary pressures during inspiration with a resultant increase in transmural pressure.\(^12\) In this context, 2 hypotheses have been advanced to explain the effect of the nasal strip on EIPH. First, the nasal strip may stabilize soft tissue rostral to the naso-incisive notch, thereby reducing a restriction to air flow during inspiration. Second, external support of this region may lessen the tendency for airways to narrow during foreleg foot fall. In either scenario, the nasal strip would decrease inspiratory resistance and perhaps lower pulmonary capillary transmural pressures during exercise, thereby lessening the severity of hemorrhage. Further studies are needed to examine the effects of the nasal strip on upper airway function and elucidate the mechanism of its effect on EIPH.
Our study also demonstrated that furosemide is effective in the amelioration of EIPH. These results lend support to the findings of Pascoe et al., who reported that furosemide treatment decreased bleeding, as assessed by postexercise endoscopic examination of the trachea, in 28 of 44 (64%) racehorses. In one other study that has used the BAL method for assessment of EIPH, furosemide administration (250 mg i.v.) 30 minutes before exercise was associated with a small, but statistically significant reduction in the RBC count in BAL fluid of horses that completed a 1,600 meter gallop on a track. On the other hand, in contrast to the results of the present study, this effect of furosemide was not apparent when furosemide was administered 4 hours before exercise. However, detection of a statistically significant effect of furosemide may have been limited by the relatively mild pulmonary hemorrhage observed in the horses of the Lester et al. study under control conditions. The mean BAL fluid RBC count in the control trial (no treatment before exercise) was only 2.3 × 10⁶/ml compared with a mean of more than 60 × 10⁶/ml in the control trial of the present study.

The effect of furosemide on pulmonary vascular pressures has provided a theoretical framework for the use of the drug in the prevention or attenuation of EIPH. A number of studies have shown that furosemide attenuates the exercise-induced increases in right atrial, pulmonary artery, and estimated pulmonary capillary pressures of horses. Very high pulmonary vascular pressures with resultant stress failure of the blood gas barrier have been proposed as the mechanism of EIPH. Indeed, there is some in vivo evidence of a relationship between pulmonary transmural capillary pressure and the severity of hemorrhage. Accordingly, a furosemide-induced attenuation of pulmonary vascular pressures could reduce pulmonary capillary endothelial disruption, thereby decreasing bleeding. It has also been suggested that extravascular effects of furosemide, such as bronchodilation, may mediate the drug's effect on the severity of EIPH. However, in clinically normal horses, furosemide did not alter respiratory mechanics during graded treadmill exercise.

In conclusion, both an external nasal strip device (FLAIR®) and furosemide significantly attenuated pulmonary hemorrhage in Thoroughbred horses following a 2 minute bout of high speed treadmill exercise. Although the direct effects of EIPH on exercise performance are unknown, the chronic pulmonary inflammatory response associated with repeated episodes of intrapulmonary bleeding may adversely affect lung health. In this regard, use of effective prophylactic treatments during training and racing may help to minimize pulmonary damage and its attendant effects on performance. Given the purported ergogenic effects of furosemide, and the general concerns associated with drug use in racehorses, the external nasal strip is a viable alternative for the attenuation of EIPH.

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References and Footnotes


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