Effect of the Sequential Administration of Two Doses of Furosemide on Exercise-Induced Pulmonary Hypertension in Thoroughbred Horses

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Compared with a single 250-mg dose of furosemide given intravenously 4 h prior to exercise, the administration of two sequential intravenous doses of furosemide (4 and 2 h prior to exercise) does not cause further attenuation of exercise-induced pulmonary capillary hypertension in Thoroughbred horses exercising at their maximal heart rate. Therefore, the sequential administration of two doses of furosemide may not affect the incidence or severity of exercise-induced pulmonary hemorrhage more than the administration of a single dose of furosemide. Authors’ address: Depts. of Veterinary Clinical Medicine (Goetz) and Veterinary Biosciences (Manohar), University of Illinois at Urbana-Champaign, 1008 W. Hazelwood Dr., Urbana, IL 61802. © 1998 AAEP.

1. Introduction
The prevalence of exercise-induced pulmonary hemorrhage (EIPH) in competitive athletes is quite high; greater than 75% of racing Thoroughbred horses have been reported to experience EIPH.1 It is well known that pulmonary arterial, capillary, and venous blood pressures increase dramatically in strenuously exercising horses.2-5 Recent research has shown that EIPH probably occurs as a result of the stress failure of pulmonary capillaries, caused by the high transmural pulmonary capillary pressure observed during intense exercise.4,6

Several studies have demonstrated a significant reduction in the exercise-induced rise in the pulmonary capillary blood pressure of horses that have been premedicated with furosemide6 (250 mg IV) 4 h prior to strenuous exertion3,7-9. Furosemide’s pulmonary hemodynamic effects have been thought to occur as a result of a diuretic-induced decrease in plasma volume or as a result of pulmonary vasodilation induced by the release of vasodilator prostaglandins. However, recent studies have shown that prostaglandins may not play a role in mediating the pulmonary hemodynamic effects of furosemide in horses exercising at their maximal heart rate.8,9 In these studies,8,9 it was observed that the attenuating effect of furosemide on the exercise-induced pulmonary capillary hypertension during strenuous exercise was unaffected by the concomitant administration of a potent cyclo-oxygenase inhibitor (flunixin meglumine).

The diuretic-induced reduction in plasma volume is reported to be greatest 15–30 min following the intravenous administration of furosemide.10 After this period, plasma volume recovers toward the pre-furosemide values. By 2 and 4 h following the intravenous administration of furosemide, plasma volume has recovered by approximately 2% and 5%, respectively.10 If furosemide decreases the magni-
tude of the pulmonary capillary hypertension in strenuously exercising horses by reducing the plasma volume, we hypothesized that the strategic administration of a second dose of furosemide as plasma volume begins to recover may further decrease the magnitude of the exercise-induced pulmonary capillary hypertension and thereby affect the incidence or severity of EIPH. This study was undertaken to test this hypothesis.

2. Material and Methods

Experiments were carried out on seven healthy, sound, exercise-trained Thoroughbred horses (six geldings and one mare), which were 3–6 years of age and weighed 431.7 ± 14.7 kg (mean ± 1 SEM). The horses were housed in an air-conditioned building with the temperature maintained at 18–20°C. They were fed a ration of alfalfa hay and oats and had free access to water. A split-plot experimental design was used in these studies. Heart rate, right atrial, and pulmonary vascular (arterial, capillary, and venous) pressures were determined by using standard techniques. Hemodynamic data were obtained at rest and during strenuous exercise performed at 14.2 m/s on a treadmill set on a 3.5% uphill grade. This workload elicited the horses’ maximal heart rates.

All horses were studied on four separate occasions, namely, a control study (no medications), a single-dose furosemide study, a low double-dose furosemide study, and a high double-dose furosemide study. The experiments were done in random order and were separated by 7 days. Horses in the control study did not receive any medications, nor was their food or water intake restricted prior to exercise.

Horses in the single-dose furosemide study received a 250-mg dose of furosemide intravenously 4 h before exercise. This dose amounted to 0.58 ± 0.02 (mean ± 1 SEM) mg/kg of body weight. This dosage regimen was adopted from Illinois horse racing regulations, which allow bleeders to receive furosemide 250 mg IV regardless of body weight 4 h prior to racing. Following the administration of furosemide, horses were kept in an empty stall without access to food or water for the next 3 h, at which time they were instrumented for hemodynamic studies. Exercise began exactly 4 h after the administration of furosemide.

Horses in the low double-dose furosemide study were managed in exactly the same fashion as in the single-dose study, with the exception that 2 h after the first dose of furosemide an additional 250 mg dose of furosemide was administered intravenously. Exercise was begun exactly 2 h after the administration of the second dose of furosemide.

Horses in the high double-dose furosemide study received a 2 mg/kg dose of furosemide 4 h before exercise. Thereafter, they were managed in the same fashion as the horses in the low double-dose furosemide study. In the high double-dose furosemide study, exercise also began exactly 2 h after the second dose (250 mg IV) of furosemide.

The nasopharynx, larynx, and the trachea (down to the carina) were examined with a flexible fiberoptic endoscope at 30 and 60 min following exercise. Exercise-induced pulmonary hemorrhage was diagnosed when fresh blood was found in the trachea.

Data were subjected to a split-plot design, repeated measures analysis of variance to determine the significant effects of treatments. Comparisons among treatments were carried out by using the least-squares significant difference method. A probability level of p < 0.05 was regarded as being statistically significant. The data are presented as mean ± 1 SEM.

3. Results

Incremental exercise resulted in progressive increases in heart rate and in mean right atrial, pulmonary arterial, pulmonary capillary, and pulmonary venous blood pressures in the control study. Exercise at 14.2 m/s on a 3.5% uphill grade elicited the maximal heart rate (217 ± 3 beats/min vs. 35 ± 2 beats/min at rest), and significant (p < 0.05) increases in mean right atrial (exercise = 60 ± 3 Torr; rest = 8 ± 1 Torr), mean pulmonary arterial (exercise = 108 ± 5 Torr; rest = 28 ± 1 Torr), mean pulmonary capillary (exercise = 88 ± 3 Torr; rest = 25 ± 1 Torr), and mean pulmonary venous (exercise = 67 ± 3 Torr; rest = 21 ± 1 Torr) pressures. There were no significant differences in heart rate at rest or during exercise performed at 14.2 m/s on a 3.5% uphill grade among the four experimental treatment groups.

Four hours after the administration of furosemide, the mean right atrial pressure of standing horses in the single-dose furosemide study was not different than that in the control study. In contrast, the mean right atrial pressure in both double-dose furosemide studies decreased (p < 0.05) compared with those in the control study. During exercise, the mean right atrial pressure increased (p < 0.05) to a similar value in the three furosemide treatment groups, and these values were significantly less (p < 0.05) than those in the control study. The mean pulmonary arterial, capillary, and venous pressures of standing horses were not different among the four treatment groups. During exercise, the mean pulmonary arterial, capillary, and venous pressures in the single-dose and high double-dose furosemide treatment groups were not different from each other and were less (p < 0.05) than those in the control study. Interestingly, the mean pulmonary arterial, capillary, and venous pressures of exercising horses in the low double-dose furosemide treatment group were not different than those in the control study.

Endoscopically, five out of seven, four out of seven, seven out of seven, and three out of seven horses experienced EIPH in the control study, single-dose...
furosemide study, low double-dose furosemide study, and high double-dose furosemide study, respectively.

4. Discussion

Our data demonstrated that the administration of an additional dose of furosemide does not decrease the mean pulmonary capillary blood pressure of strenuously exercising Thoroughbred horses more than a single dose of furosemide. Thus, these observations do not support the hypothesis that the strategic administration of a second dose of furosemide, as plasma volume begins to recover, further decreases the magnitude of the exercise-induced pulmonary capillary hypertension in strenuously exercising Thoroughbred horses. It appears that the extra fluid loss induced by the diuretic effect of the second dose of furosemide is likely offset by fluid movements from the interstitial, intracellular, and gastrointestinal compartments.

The postexercise endoscopic findings tended to support the observations regarding mean pulmonary capillary blood pressure made during exercise. The mean pulmonary capillary blood pressure during exercise at 14.2 m/s on an uphill grade of 3.5% in the low double-dose furosemide study tended to be greater than that in the single-dose as well as the high double-dose furosemide studies (note that pressures in the single-dose and high double-dose furosemide studies were not different from each other). In keeping with these data, the incidence of endoscopically confirmed EIPH was also found to be greater in the low double-dose furosemide study (seven out of seven horses experienced EIPH) than in the single-dose and high double-dose furosemide studies, in which four out of seven and three out of seven horses experienced EIPH, respectively.

5. Conclusions

In conclusion, the mean pulmonary capillary blood pressure data and the endoscopic findings in the present study suggest that the administration of a second dose of furosemide is unlikely to affect the incidence or severity of exercise-induced pulmonary hemorrhage in racing Thoroughbred horses. This research was supported by grants-in-aid from the Illinois Department of Agriculture Equine Research Fund and the Illinois Thoroughbred Horsemen’s Association. The treadmill at the University of Illinois was procured with the financial support provided by the Illinois Thoroughbred and Standardbred Breeder’s Fund.

References and Footnotes

5. Manohar M, Hutchens E, Coney E. Pulmonary vascular pressures of Thoroughbreds increase rapidly and to a higher level with rapid onset of high intensity exercise than with slow onset. Equine Vet J 1994;26:496–499.

Lasix, Hoechst Roussel Agri-Vet, Somerville, NJ 53211.