Complete Cyclooxygenase Inhibition with Phenylbutazone Does Not Mitigate the Attenuating Effect of Furosemide on Pulmonary Vascular Pressures of Strenuously Exercising Thoroughbred Horses

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Complete cyclooxygenase inhibition with phenylbutazone before administration of furosemide does not alter the attenuating effect of furosemide on pulmonary capillary hypertension in strenuously exercising Thoroughbred horses, and therefore, should not predispose horses so treated to an increased incidence/severity of exercise-induced pulmonary hemorrhage. Authors’ address: Depts. of Veterinary Clinical Medicine and Veterinary Biosciences (Manohar), College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61801. © 1999 AAEP.

1. Introduction
Exercise-induced pulmonary hemorrhage (EIPH) is known to occur in greater than 75% of racing Thoroughbred horses¹ and may decrease performance. Studies have shown that pulmonary arterial, capillary, and venous blood pressures increase dramatically in strenuously exercising horses.²⁻⁵ Current evidence suggests that EIPH probably occurs as a result of stress failure of pulmonary capillaries.⁶ Capillary stress failure results from the high transmural pulmonary capillary pressure which occurs during strenuous exertion.⁶ Administration of furosemide before strenuous exertion decreases pulmonary vascular pressures and may thereby decrease the incidence/severity of pulmonary bleeding in horses afflicted with EIPH.³,⁷,⁸ Furosemide’s pulmonary hemodynamic effects have been thought to occur as a result of a diuretic-induced decrease in plasma volume and/or as a result of pulmonary vasodilation induced by release of vasodilator prostaglandins.⁹ Phenybutazone is a nonsteroidal anti-inflammatory drug that is frequently used in the management of acute and chronic musculoskeletal infirmities of equine athletes.¹⁰ The drug manifests its clinical effects by inhibiting cyclooxygenase,¹⁰ an enzyme involved in the synthesis of prostaglandins which are known to increase markedly in strenuously exercising horses.¹¹ An important unanswered question is, could phenylbutazone treatment of racehorses partially reverse the furosemide-induced attenuation of pulmonary vascular hypertension, thereby leading to an increase in the incidence/severity of EIPH? Although it has been shown that
cessation of phenylbutazone treatment 24 hours before the administration of furosemide was not associated with such an effect, it should be recognized that by 24 hours postadministration, phenylbutazone’s anticyclooxygenase effect may have decreased to negligible levels.

The primary objective of the present study was to examine the effects of complete cyclooxygenase inhibition with phenylbutazone on furosemide-induced attenuation of right atrial and pulmonary arterial, capillary, and venous blood pressures of Thoroughbred horses at rest and during high-intensity treadmill exercise.

2. Materials and Methods

Experiments were carried out on 8 healthy, sound Thoroughbred horses (3 mares and 5 geldings), with known histories of EIPH which were 2–4 years old and weighed from 409 to 478 kg. The horses were housed in an air-conditioned building (18–20°C). They were fed a ration of alfalfa hay and oats, and free access to water was provided. A split-plot experimental design was used in these studies. Heart rate, right atrial, and pulmonary vascular (arterial, capillary, and venous) pressures were determined using catheters with tip manometers. Hemodynamic data were obtained at rest and while galloping at 14.5 m/s on a treadmill set at a 5% uphill grade for 90 seconds. This workload elicited maximal heart rate (225 ± 3 beats/min).

All horses were studied following 3 different treatments; namely, a control study (no medications), a furosemide study without administration of phenylbutazone, and a phenylbutazone + furosemide study. Experiments on each horse were separated by 7–10 days and were carried out in random order. Furosemide was administered per Illinois Horse Racing Regulations (250 mg IV 4 hours pre-exercise regardless of body weight). Following furosemide administration, horses were denied access to water until completion of the hemodynamic study. Horses in the phenylbutazone + furosemide experiments received 5 IV injections of phenylbutazone (4.4 mg/kg) at 12 hour intervals. This phenylbutazone dosage regimen completely inhibits the action of cyclooxygenase. Immediately after the 5th injection of phenylbutazone, horses received 250 mg of furosemide intravenously.

The data were subjected to a split-plot design analysis of variance to determine the significant effects of treatments. Comparisons among treatments were carried out 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

In the control studies at rest, values of heart rate, mean right atrial pressure, mean pulmonary arterial pressure, mean pulmonary capillary pressure, and mean pulmonary venous pressure were 40 ± 3 beats/min, 7 ± 2, 36 ± 2, 31 ± 2, and 25 ± 2 mm Hg, respectively. Exercise resulted in a highly significant (\( p < 0.001 \)) increase in heart rate, as well as right atrial and pulmonary vascular pressures. During galloping at 14.5 m/s on a 5% uphill grade, heart rate, mean right atrial pressure, mean pulmonary arterial pressure, mean pulmonary capillary pressure, and mean pulmonary venous pressures were 225 ± 3 beats/min, 55 ± 5, 98 ± 5, 81 ± 4, and 64 ± 3 mm Hg, respectively.

In the furosemide-only experiments, the mean pulmonary venous pressure decreased significantly, (\( p < 0.05 \)) at rest compared to control measurements. As in the control experiments, exercise performed at 14.5 m/s on a 5% uphill grade also resulted in significant (\( p < 0.001 \)) increases in heart rate, mean right atrial pressure, and mean pulmonary vascular pressures. During exercise at 14.5 m/s on a 5% uphill grade, heart rate was unchanged after furosemide administration, but a statistically significant (\( p < 0.05 \)) attenuation of the exercise-induced rise in mean right atrial pressure, mean pulmonary arterial, capillary, and venous pressures was observed. The values for mean right atrial, pulmonary arterial, capillary, and venous pressures were 86%, 91%, 85%, and 76% respectively, of the corresponding values in the control study.

Measurements obtained from quietly standing as well as exercising horses in the phenylbutazone + furosemide experiments closely resembled data in the furosemide-only experiments; statistically significant differences between these treatments were not observed at rest or during strenuous exercise performed at maximal heart rate (14.5 m/s on a 5% uphill grade).

4. Discussion

Our data in the control study confirm earlier findings that exercising Thoroughbred horses develop pulmonary arterial, capillary, and venous hypertension, and that intravenous administration of furosemide attenuates the exercise-induced rise in mean pulmonary vascular pressures. Thus, furosemide administration may help limit the incidence/severity of EIPH as the transmural force exerted on the pulmonary capillaries is significantly diminished.

The new findings in the present study include the observations that complete cyclooxygenase inhibition with phenylbutazone prior to administration of furosemide does not significantly affect furosemide’s pulmonary hemodynamic effects in quietly standing or strenuously exercising horses. These observations are in agreement with data obtained using another nonsteroidal anti-inflammatory agent—flunixin meglumine—and should help alleviate the concerns of racetrack veterinarians in that the beneficial pulmonary hemodynamic effects (i.e., significant attenuation of the exercise-induced pulmonary capillary hypertension) of furosemide in “bleeders”
are likely to remain unaffected by concomitant treatment with nonsteroidal anti-inflammatory agents. Because the dosage regimen for phenylbutazone administration used in the present study is known to cause complete cyclooxygenase inhibition, one can also be assured that smaller doses of phenylbutazone should not negate the attenuating effect of furosemide on the pulmonary capillary blood pressure of exercising horses. These findings differ from those in another study where it was reported that treatment with flunixin meglumine and phenylbutazone partially reversed the furosemide-induced attenuation of pulmonary arterial hypertension in exercising horses. These differences may have occurred because the catheter-tipped manometers in that study were not referenced. Also, in that study, pulmonary capillary or venous pressures were not measured. Because phenylbutazone (like flunixin meglumine) is a known potent inhibitor of cyclooxygenase in horses, we concluded that the pulmonary hemodynamic effects of furosemide in exercising horses are probably not mediated via release of prostaglandins.

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References and Footnotes

5. Manohar M, Coney E, Hutchens 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.

*Millar Instruments Inc., Houston, TX 77023-5423.
*Lasix®, Hoechst-Roussel Agri-Vet Co, Sommerville, NJ 08876.
*Vedco, St. Joseph, MO 64504.
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