Exercise-Induced Arterial Hypoxemia in Thoroughbreds Is Not Affected by Administration of the H₁ Histamine Receptor Antagonist Tripelennamine Hydrochloride

Thomas E. Goetz, DVM, Diplomate ACVIM; Murli Manohar, BVSc, PhD; Sarah Humphrey, BS; and Tracy DePuy, BS

Exercise-induced arterial hypoxemia (EIAH) in human subjects may be associated with pulmonary injury/capillary stress failure-induced histamine release and is reported to be ameliorated by administration of H₁ antihistaminics. EIAH is a routine occurrence in strenuously exercising Thoroughbreds, 75–100% of which also experience exercise-induced pulmonary hemorrhage (EIPH). In contrast with reports in human subjects, our data revealed that pre-exercise administration of intravenous tripelennamine hydrochloride (an H₁ histamine receptor antagonist) had no affect on EIAH, desaturation of hemoglobin, hypercapnia, or acidosis. The failure of an intravenously administered H₁ receptor antagonist to significantly modify EIAH suggests that pulmonary injury-induced histamine release may not play a major role in causing EIAH in Thoroughbred horses.

Authors’ addresses: University of Illinois, College of Veterinary Medicine, Urbana, IL 61802. © 2002 AAEP.

1. Introduction

Exercise-induced arterial hypoxemia (EIAH) occurs in humans¹,² and horses.³–¹² In both species, EIAH has been reported to limit exercise performance.¹,²,⁶,¹² The mechanism(s) responsible for the development/severity of equine EIAH continue to be debated¹,²,⁷ and have included the following: “relative” alveolar hypoventilation (evidenced by significant arterial hypercapnia in exercising horses despite increased alveolar ventilation), ventilation:perfusion mismatching, and diffusion limitation related to the significantly shortened transit time for blood in the pulmonary capillaries as cardiac output increases dramatically.⁴–⁹,¹¹,¹²

It was recently demonstrated in human subjects experiencing EIAH that stress failure of pulmonary capillaries (leading to EIPH during heavy exercise¹³) is accompanied by significant histamine release,¹⁴,¹⁵ possibly from airway mast cells, in response to pulmonary injury/inflammation.²,¹⁴,¹⁶ Further work has revealed that the stabilization of airway inflammatory/mast cells to prevent the release of histamine with inhaled nedocromil sodium (an inflammatory/mast cell stabilizer¹⁷ used for management of asthma) or IV administration of an H₁ receptor antagonist (diphenhydramine hydrochloride) could attenuate¹⁶,¹⁸ or ameliorate¹⁹ EIAH in human subjects. These observations suggest that histamine release after pulmonary injury²,¹⁴–¹⁶ may play a role...
in the development of EIAH, however, a definitive causal relationship has yet to be established. It has been speculated that the potent capillary permeability-enhancing effects of histamine (through stimulation of H₁ receptors) contribute to EIAH by causing pulmonary edema and thereby adversely affecting the distribution of ventilation:perfusion within the lungs.²⁻⁴⁻¹⁶⁻¹⁸

These observations in humans are pertinent to racehorses because the transmural pulmonary capillary forces exerted on the blood-gas barrier of exercising horses greatly exceed that in exercising human subjects, resulting in a high incidence (>75%) of capillary stress failure-induced EIPH.²⁶⁻²⁸

For these reasons, the severity of lung injury and the ensuing interstitial pulmonary edema may be more pronounced in racehorses.²⁸ Presently, it is not known whether airway histamine release in response to capillary stress failure-related pulmonary injury also contributes to the phenomenon of EIAH in horses. Therefore, our primary objective in this study was to examine the effects of an IV administered H₁ receptor antagonist, tripeledennamine HCl, on EIAH in Thoroughbred horses performing short-term high-intensity exercise that induced EIPH. Our hypothesis was that pre-exercise antihistaminic administration may prevent histamine (released from airway inflammatory/mast cells during exercise) from exerting its effects on pulmonary capillary permeability, thereby preventing the development of interstitial pulmonary edema, which may attenuate/ameliorate EIAH.

2. Materials and Methods

Experiments were carried out on seven healthy, sound, 3- to 6-yr-old Thoroughbred horses (three fillies and four geldings), weighing 460 ± 18 kg. The horses were exercise-trained for a period of 7 wk before the blood-gas studies were undertaken. They were housed in an air-conditioned building and were accustomed to being handled by people. The horses were fed a ration that consisted of alfalfa hay and oats, and they had free access to water. The horses were dewormed periodically and were inoculated with tetanus toxoid and strangles vaccine. Our protocols and procedures were approved by the Institutional Laboratory Animal Care and Use Committees.

Initially the horses were exercised for 4 wk (3 d/wk) in the following manner, with the treadmill set on the flat (0% grade). Exercise began with a walk at 2 m/s for 120 s. Subsequently, belt speed was increased 1 m/s every 60 s until the horse had trotted at 6 m/s for 60 s. Treadmill speed was then increased to 8 m/s, and the horses were cantered for 60 s. The horses were then galloped, first at 10 m/s for 60 s and thereafter at 14 m/s for 120 s. Belt speed was then decreased, first to 5 m/s for 60 s and then to 2 m/s for 5 min before stopping the treadmill. After completing 4 wk of exercise training in this manner, the horses were exercised for 3 wk using the same incremental exercise regimen 3 d/wk, but the treadmill was set at a 3.5% uphill grade.

It should be noted at the outset that because occurrence of EIPH shows that capillary stress failure-related pulmonary injury has indeed occurred, we intended to use a workload capable of eliciting EIPH consistently. In separate trials carried out after completing 7 wk of exercise training, it was observed that galloping at 14 m/s on a 3.5% uphill grade elicited maximal heart rate and induced EIPH in all horses. Thus, this workload was selected for further experimentation in this study.

All horses were studied in the control as well as the tripeledennamine hydrochloride experiments. The sequence of control and tripeledennamine hydrochloride experiments was randomized for every horse, and 7 d were allowed between treatments. Ambient temperature in the laboratory was maintained at 19–20°C, and all exercise was performed with the treadmill set at a 3.5% uphill grade.

In the placebo/control study, blood-gas/pH measurements were first made in duplicate on quietly resting horses (before any medications had been administered) when heart rate and pulmonary vascular pressures had been stable for 10–15 min. From this point on, these data will be referred to as pre-placebo/placebo rest. After completing pre-placebo/drug rest measurements, 250 ml of physiological saline was administered intravenously. About 12–14 min later, blood-gas/pH measurements were made (in duplicate) on resting horses. From this point on, these data will be referred to as post-placebo/placebo rest. Exactly 15 min post-placebo injection, horses were exercised in the same manner as during exercise training (described above) with the treadmill set a 3.5% uphill grade. During exercise, along with continuous core temperature measurement, simultaneous arterial and mixed-venous blood samples were obtained for determining blood-gas tensions, pH, hemoglobin (Hb) concentration, Hb-O₂ saturation, and O₂ content at 55 s of trotting at 6 m/s, at 55 s of exercise at 8 m/s, at 30, 60, 90, and 120 s of galloping at 14 m/s on a 3.5% uphill grade, and at 120 s of walk at 2 m/s.

The tripeledennamine hydrochloride experiments were conducted in exactly the same manner as the control experiments except that tripeledennamine hydrochloride (1.10 mg/kg body weight dissolved in 250 ml of physiological saline) was administered IV instead of saline.

In both treatments, careful examination of the nasopharynx, larynx, and trachea (down to the carina) was undertaken 45–50 min post-exercise using a flexible fiberoptic endoscope. The presence of fresh blood in the trachea was regarded as evidence of the occurrence of EIPH. Our procedures for measurement of blood gases and pulmonary vascular pressures have been described in considerable detail previously, therefore, only a brief description is given here.

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the study, after local infiltration of 2% lidocaine hydrochloride in the 17th intercostal space, the abdominal aorta was percutaneously catheterized.\textsuperscript{6,8,9} Thereafter, using local infiltration of 2% lidocaine hydrochloride, cardiac catheters (8F) equipped with a tip-manometer,\textsuperscript{7} fluid-filled lumen,\textsuperscript{5} and thermistor\textsuperscript{6} were advanced into the pulmonary artery through introducers inserted into the left jugular vein. The locations of various catheters were confirmed by monitoring the characteristic phasic blood pressure waveforms on an oscillographic recorder.\textsuperscript{6} Besides blood pressure monitoring, these catheters permitted simultaneous sampling of the aortic and pulmonary arterial (mixed-venous) blood as well as continuous monitoring of the pulmonary arterial blood (core) temperature during the experiments. After catheter placement, horses stood quietly on the treadmill for approximately 45–50 min before blood-gas/pH studies were undertaken.

Blood-gas tensions, pH, Hb concentration, Hb-O\textsubscript{2} saturation, and O\textsubscript{2} content were determined using a carefully calibrated blood-gas analyzer/co-oximeter\textsuperscript{5,7} and all blood-gas tensions/pH data were corrected to the simultaneously measured pulmonary artery blood temperature. The calibration of our blood-gas/pH analyzer/co-oximeter was checked frequently and verified using tonometered solutions of known blood-gas tensions, pH, Hb concentration, and O\textsubscript{2} saturation. In this study, the O\textsubscript{2} extraction (%) was calculated as follows: (arterial to mixed venous blood O\textsubscript{2} content gradient/arterial O\textsubscript{2} content) $\times 100$.

All data were subjected to repeated measures, split plot design analysis of variance using the SAS statistical software package,\textsuperscript{6} and the treatment comparisons were made using the least-squares significant difference method.\textsuperscript{30} Data for the placebo (control) as well as the tripelennamine hydrochloride experiments were also individually subjected to analysis of variance followed by Newman-Keuls multiple range test\textsuperscript{30-32} to determine the significant effects of work intensity/duration within each treatment. For all statistical analyses, the level of significance was set at $p < 0.05$. The statistical power of comparisons for variables in this study exceeded 80%. The data are presented as mean $\pm$ SEM.

3. Results

General Clinical Observations

Immediately after IV administration of tripelennamine hydrochloride, the horses became very alert and seemed somewhat agitated. During this period, the horses typically raised their head, tightened their neck muscles, had excessive and rapid eye and ear movements, bit at the air, snorted, briskly swished their tail, and stomped and pawed with their front feet. Concomitant with this period of excitement was a sudden significant rise in Hb concentration (see Arterial and Mixed-Venous Blood O\textsubscript{2} Content), an increase in heart rate (the pre-drug resting heart rate doubled), and development of marked systemic and pulmonary hypertension. The latter changes were presumed to be associated with sympathoadrenal activation associated with CNS excitement, resulting in splenic contraction, vasoconstriction, and possibly, increased cardiac output. During exercise, Hb concentration, heart rate, and pulmonary and systemic blood pressure values were not different between the placebo and tripelennamine hydrochloride experiments.

Temperature

Pre-exercise values (pre- and post-drug) of core temperature (37.4 $\pm$ 0.1°C and 37.5 $\pm$ 0.1°C) in the placebo and tripelennamine HCl treatments, respectively, were not significantly different from each other. In both treatments, core temperature increased progressively with increasing work intensity, however, the increment was significantly greater ($p < 0.0001$) in the tripelennamine HCl study. The core temperature reached 40.7 $\pm$ 0.1°C and 41.2 $\pm$ 0.1°C in the placebo and tripelennamine HCl experiments, respectively, at 120 s of galloping at 14 m/s on a 3.5% uphill grade.

Arterial O\textsubscript{2} Tension and Hb-O\textsubscript{2} Saturation

Pre-drug resting data for these variables were similar in both treatments. In resting horses, these variables were unaffected by tripelennamine HCl administration. During sub-maximal exercise at 6 and 8 m/s, arterial O\textsubscript{2} tension and Hb-O\textsubscript{2} saturation did not change.

Arterial O\textsubscript{2} tension decreased significantly ($p < 0.0001$) at 30 s of galloping at 14 m/s on a 3.5% uphill grade in both treatments, however, further statistically significant changes did not occur as exercise duration increased to 120 s. In the placebo and tripelennamine hydrochloride experiments, the arterial O\textsubscript{2} tensions at 120 s of galloping at 14 m/s on a 3.5% uphill grade were 71.3 $\pm$ 2.8 and 71.3 $\pm$ 2.2 mm Hg, respectively. There were no statistically significant differences between the placebo and tripelennamine hydrochloride experiments during the exercise protocol.

Statistically significant desaturation of Hb in the arterial blood was observed at 30 s of galloping at 14 m/s on a 3.5% uphill grade in both treatments. Desaturation of Hb intensified as exercise duration progressed to 120 s, but statistically significant differences between the placebo and the tripelennamine hydrochloride studies were not found. The rightward shift of the Hb-O\textsubscript{2} dissociation curve as hypercapnia (see Arterial CO\textsubscript{2} Tension), acidosis (see Arterial pH), and hyperthermia (see Temperature) intensified with increasing exercise duration was probably responsible for the increased desaturation of arterial Hb seen in going from 30 to 120 s of galloping at 14 m/s on a 3.5% uphill grade. The arterial Hb-O\textsubscript{2} saturation values were 83.8 $\pm$ 2.7% and 80.6 $\pm$ 2.3% in the placebo and tripelennamine hydrochloride experiments, respectively, at 120 s of
galloping at 14 m/s on a 3.5% uphill grade; statistically significant differences between the treatments were not observed.

Mixed-Venous Blood O₂ Tension and Hb-O₂ Saturation
In both treatments, pre-drug values of these variables were similar. However, after tripelennamine HCl administration, a statistically significant (p < 0.001) rise in mixed-venous blood O₂ tension and Hb-O₂ saturation was observed. Work intensity-related significant reductions in these variables were observed in both treatments, but statistically significant differences between the two treatments were not found.

Arterial CO₂ Tension
Arterial CO₂ tension was not significantly affected by administration of tripelennamine hydrochloride to resting horses. In both treatments, horses hyperventilated during sub-maximal exercise at 6 and 8 m/s. In contrast, during galloping at 14 m/s on a 3.5% uphill grade, a significant hypercapnia developed in both treatments. The extent of exercise-induced arterial hypercapnia was similar in both treatments. Arterial CO₂ tensions were 56.2 ± 2.9 mm Hg and 60.1 ± 3.0 mm Hg in the placebo and the tripelennamine HCl treatments, respectively, at 120 s of galloping at 14 m/s on a 3.5% uphill grade.

Arterial Blood pH
Arterial pH values pre- and post-placebo/tripelennamine hydrochloride administration were not significantly different in horses at rest. Arterial pH did not change significantly in either treatment during sub-maximal exercise at 6 and 8 m/s compared with galloping at 14 m/s on a 3.5% uphill grade, where a progressive, significant acidosis of a similar magnitude was observed in both treatments. The arterial pH values were 7.090 ± 0.044 and 7.040 ± 0.030 in the placebo and the tripelennamine HCl experiments, respectively, at 120 s of galloping at 14 m/s on a 3.5% uphill grade.

Arterial and Mixed-Venous Blood O₂ Content
Pre-drug values of arterial and mixed-venous blood O₂ content in resting horses were similar in the placebo and the tripelennamine hydrochloride experiments. After tripelennamine hydrochloride administration, there was a significant (p < 0.0001) excitement-related increase in Hb concentration in resting horses (pre-drug resting value of Hb = 12.7 ± 0.5 g/dl, immediately after tripelennamine hydrochloride administration Hb = 17.7 ± 0.6 g/dl). Concomitant with the increase in Hb concentration, arterial and mixed-venous blood O₂ content also increased. Irrespective of the increases in arterial and mixed-venous blood O₂ content, the arterial to mixed-venous O₂ content gradient of resting horses after tripelennamine hydrochloride administration (4.9 ± 0.3 ml O₂/dl blood) was not found to be significantly different from the placebo (4.4 ± 0.3 ml O₂/dl blood).

In both treatments, Hb concentration increased significantly (p < 0.0001) during exercise compared with pre-drug rest, however, statistically significant differences between the treatments could not be discerned. The arterial Hb concentration was 22.2 ± 0.5 and 22.5 ± 0.5 g/dl in the placebo and the tripelennamine HCl experiments, respectively, at 120 s of galloping at 14 m/s on a 3.5% uphill grade.

The arterial blood O₂ content increased significantly (p < 0.0001) and of a similar magnitude in both treatments compared with pre-drug rest during exercise as Hb concentration increased. A corresponding work intensity-related reduction of a similar magnitude was also seen in the mixed-venous blood O₂ content of both treatments. Consequently, the arterial to mixed-venous O₂ content gradient of exercising horses increased significantly (p < 0.0001) compared with resting values reaching a similar magnitude in both treatments. The arterial to mixed-venous blood oxygen content gradient reached 23.2 ± 0.7 and 22.8 ± 0.8 ml O₂/dl of blood in the placebo and tripelennamine hydrochloride experiments, respectively, as O₂ extraction approached 91.5 ± 1.0% and 92.2 ± 0.6%, respectively, at 120 s of galloping at 14 m/s on a 3.5% uphill grade. Statistically significant differences between the two treatments were not observed in these variables during exertion.

Airway Endoscopy
All horses in both treatments experienced EIPH, demonstrated by the presence of fresh blood in the trachea after exertion.32,36,27

4. Discussion
Our observations regarding development of arterial hypoxemia, desaturation of Hb, hypercapnia, acidosis, hemoconcentration, increased O₂ extraction, and arterial to mixed-venous O₂ content gradient, as well as significant hyperthermia in horses performing short-term high-intensity exercise in the placebo study mirrored those reported previously.3–12,39

The new finding in this study was that we did not observe an improvement in arterial O₂ tension, Hb-O₂ saturation, and O₂ content of horses exercising after tripelennamine hydrochloride administration. Therefore, the arterial to mixed-venous blood O₂ content gradient and O₂ extraction during exercise performed at the same workload also remained unaffected. It is also noteworthy that the extent of exercise-induced hypercapnia as well as metabolic acidosis in our tripelennamine hydrochloride experiments was not significantly different from that in the placebo study. These observations suggest that during galloping at 14 m/s on a 3.5% uphill grade, the aerobic and anaerobic metabolic needs remained similar between the placebo and the tripelennamine hydrochloride studies. Because all horses were observed to have experienced EIPH in
both treatments, there can be no doubt that stress failure of pulmonary capillary-induced pulmonary injury had indeed occurred, yet the intravenously administered H1 receptor antagonist—tripelennamine hydrochloride, was ineffective in significantly affecting the development/severity EIAH. Thus, it seems unlikely that pulmonary injury-related airway inflammatory/mast cell histamine release plays a major role in bringing about EIAH in Thoroughbred horses.

Our findings are in contrast with observations in human subjects where administration of H1 receptor antagonists have been shown to attenuate and/or ameliorate EIAH. Although the reasons for divergent findings of this study are difficult to discern, species differences cannot be ruled out.

In the context of the development/severity of EIAH, we observed that hypoxemia was already well developed by 30 s of high-intensity exercise in the placebo as well as in the tripelementamine hydrochloride studies, and that increasing exercise duration to 120 s did not cause further statistically significant changes in the arterial O2 tension. According to the pulmonary injury/airway histamine release/interstitial pulmonary edema hypothesis, one would expect that there would be an intensification of EIAH with increasing exercise duration, as interstitial pulmonary edema (caused by the increased capillary permeability in response to airway mast cell released histamine) intensifies over time. The fact that this was not the case in this study or in previous studies using a similar exercise protocol argues against a significant role for pulmonary capillary stress failure/pulmonary injury-induced airway histamine release in causing EIAH in horses. Further, support for this argument is provided by our observations that during a successive bout of strenuous exercise performed 6 min after the first high-intensity exercise bout that caused stress failure of pulmonary capillaries/EIPH, an accretion of arterial hypoxemia could not be demonstrated.

In conclusion, our data showed that the intravenously administered H1 receptor antagonist—tripelenamine hydrochloride failed to significantly affect arterial hypoxemia and desaturation of Hb in horses performing short-term high-intensity exercise that caused stress failure of pulmonary capillaries/pulmonary injury, leading to EIPH. Thus, it seems unlikely that pulmonary injury-related histamine release plays a major role in bringing about EIAH in Thoroughbred horses. The rapid development of EIAH and the fact that its severity did not change with increasing exercise duration suggest that this phenomenon more likely has a functional basis, probably related to the significantly shortened transit time for blood in the pulmonary capillaries as cardiac output increases dramatically.

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References and Footnotes


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