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New Jersey Agricultural Experiment Station

Equine Science Center
Research Updates

Effects of a Type-5 Phosphodiesterase Inhibitor on Pulmonary Artery Pressure in Race Fit Horses

Dr. Ken McKeever, Professor of Animal Sciences and colleagues Drs. Ric Birks and Mary Durando from Equine Sports Medicine Consultants in Delaware looked at the potential use of a Type-5 Phosphodiesterase inhibitor to reduce blood pressure as a treatment for "bleeding" or exercise induced pulmonary hemorrhage (EIPH). This research was funded by Equine Sports Medicine Consultants, LLC.

The Research Project

The proposed pathophysiologic mechanism for pulmonary hemorrhage includes high pulmonary vascular pressures during strenuous maximal exercise, with resultant thickening of pulmonary vein walls and decreased luminal diameter and increased intravascular pressure at the level of the pulmonary capillaries. Some lung capillaries rupture under the high-pressure conditions that exist during heavy exercise.

Although exercise induced pulmonary hemorrhage (EIPH) has been recognized for decades, researchers still have more questions than answers when it comes to the cause and prevention of this problem.

The Rutgers Exercise Physiology Lab (pictured above during a treadmill demo) was used to test the effects of a Type-5 Phosphodiesterase Inhibitor on pulmonary artery pressure.

While research has shed light as to why horses bleed during strenuous exercise, there is no consensus regarding the true cause of EIPH.

The main controversy surrounding the use of furosemide in racehorses is whether the drug actually enhances a horse's performance ability independent of any effect on the severity of bleeding. Horses lose weight after receiving furosemide four hours before race time.

The reduction in body weight is due to increased urination and water loss, coupled with the fact that horses have restricted access to feed and water for the four hours prior to racing, can result in significant weight loss (15-20 pounds). This can result in an exercise performance advantage over horses not receiving furosemide.

Ideally, a solution to the treatment of EIPH would be one that effectively lessens the severity of bleeding without performance enhancing effects that one sees with furosemide. Because EIPH is believed to be caused

by an increase in blood pressure during strenuous exercise, treating the horse prior to racing with an agent that actually lowers blood pressure would be ideal.

This study was performed to determine the optimal dose and timing of E4021 (EIPHISOLTM) to reduce pulmonary artery pressure (PAP) during treadmill exercise. Eight (4 geldings, 4 mares) unfit Standardbreds (4-8 years of age, and approximately 490 kg body weight) were conditioned for the entire trial. Speed and duration increased weekly until weeks 12-14, when three treadmill Graded Exercise Tests (GXT) were performed to document stable fitness (VO2max). Two randomized crossover experiments then used Simulated Race Tests (SRT) to determine the optimal dose and timing of IV administration of E4021 prior to exercise.

In the first experiment, researchers evaluated the effect of two doses of the drug (50 versus 100 mg) and administration at two time points (45 versus 90 minutes prior to exercise) and compared this to the control group which received no drug.

In experiment 2, all treated horses received drug treatment at 90 minutes prior to exercise, compared to the control group which received no drug. The effect of three drug doses were compared: 100 mg; 150 mg; or 200 mg. The SRT used a two minute warm-up followed by two minutes at 110% VO2max; followed by a two minute recovery period. Pulmonary artery pressure, electrocardiographs, VO2, and VCO2 were measured continuously and blood samples (3 mL) were collected anaerobically at the end of the warm-up; and at one and two minutes during race speed, and at the end of recovery to measure partial pressure of oxygen in arterial blood; partial pressure of carbon dioxide; pH; arterial oxygen saturation; concentrations of the electrolytes sodium, potassium, and calcium; concentrations of lactate, glucose, and hemoglobin; and packed cell volume or hematocrit.

The major finding was that the 100 mg dose administered 90 minutes before exercise resulted in the lowest pulmonary artery pressure.

There were no differences in pulmonary artery pressure in experiment 2 which compared the doses of 100 mg, 150 mg, and 200 mg of drug given 90 minutes prior to exercise.

While E4021 did lower pulmonary artery pressure when given at the dose of 100 mg 90 minutes before exercise, it did not alter markers of aerobic or anaerobic performance. The reduction of pulmonary artery pressure of approximately 30 mmHg seen with 100 mg dose at 90 minutes prior to exercise represents a clinically significant effect.

Conclusions and Future Directions:

The reduction of pulmonary artery pressure of approximately 30 mmHg seen with 100 mg dose at 90 minutes prior to exercise represents a clinically significant effect as the reduction in pulmonary blood pressure falls below the recognized threshold for capillary stress failure in the lungs of strenuously exercised horses.

Future directions are dependent upon funding and requests from the FDA as part of the approval process. Potential studies will include field trials and treadmill experiments using clinically affected horses.

Meet the Researchers

Dr. Ken McKeever
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Ken McKeever received his B.S. degree and M.S. degrees in Animal Science from California State Polytechnic University Pomona and Fresno State University. Following completion of his Masters he worked as the Assistant Manager of Post-Time Thoroughbred Ranch in Tulare, California. McKeever earned his Ph.D. in Animal Physiology at the University of Arizona where he also managed the University Horse Center and Quarter Horse breeding program.

Upon completing his Ph.D. McKeever served for two years as a National Academies of Sciences-National Research Council Resident Research Associate in the Cardiovascular Research Lab at the NASA Ames Research Center in California. From 1987 to 1994 Dr. McKeever developed and coordinated research at the Equine Exercise Physiology Laboratory at the Ohio State University.

In 1995 he joined the Faculty in the Department of Animal Sciences at Rutgers University as an Associate Professor and proceeded to build, develop, and coordinated one of the most active Equine Exercise Physiology laboratories in the USA. Dr. McKeever earned the rank of Full Professor in 2009 and currently serves as Associate Director of the Rutgers University Equine Science Center.

He currently serves as President of the Equine Science Society as well as the Editor-in-Chief of the journal Comparative Exercise Physiology. On a basic level his research has focused on comparative exercise and cardiovascular physiology with a particular interest in the effects of aging on the integration of the cardiovascular, renal, and endocrine systems in the control of blood pressure, blood volume and fluid and electrolyte balance.

On an applied level, his research has focused on the effects of performance enhancing practices on the physiological responses of the equine athlete. These studies are just part of the more than 200 book chapters, journal articles and proceedings papers, and more than 60 abstracts that have advanced our understanding of the athletic horse.

In his spare time, he plays water polo goalie at the local, national, and international level and is also an amateur genealogist and historian.

Further Readings:

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Takahashi, T.; Hiraga, A.; Ohmura, H.; Kai, M.; Jones, J.H. Frequency and risk factors for epistaxis associated with exercise-induced pulmonary hemorrhage in horses: 251,609 race starts (1992-1997). Journal of the American Veterinary Medical Association, 218, 1462-1464, 2001.

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