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AN INTERIM REPORT ON THE TESTING INTEGRITY PROGRAM SEMINAR "FUROSEMIDE IN THE HORSE: ITS ACTIONS, EFFECTS AND ITS REGULATORY CONTROL"

HELD AT

THE NEW ORLEANS HILTON RIVERSIDE

MARCH 1, 1998

Convened By: Dr. Richard Sams & Dr. Scott Stanley

Edited By : Wyndee Carter, J. D. Harkins & Thomas Tobin

Table of Contents

Participants	Affiliations
Dr. Thomas Tobin	University of Kentucky
Dr. Richard Sams	The Ohio State University
Dr. Lawrence Soma	University of Pennsylvania
Dr. Theodore Hill	New York Jockey Club
Dr. Ron Jensen	California Horse Racing Board
Dr. Gary Norwood	American Assoc. Of Equine Practitioners
Dr. Mitzi Fisher	Kentucky Racing Commission
Dr. Charles Short	Louisiana State University
Dr. Wayne Skinner	University of California, Davis
Dr. Allen Ray	Texas A&M University
Dr. Cornelius Uboh	Westchester State College
Dr. Scott Stanley	University of California, Davis
Dr. Fritz Lehner	University of Kentucky
Mr. Shawn Magsig	Neogen Corporation, Lexington
Dr. Steve Barker	Louisiana State University
Dr. Cynthia Kolias-Baker	University of California, Davis
Mrs. Petra Harman	Industrial Laboratories, Denver
Mr. Mike Burleson	Texas Racing Commission

Executive Summary

- **Exercise Induced Pulmonary Hemorrhage (EIPH)** is caused by rupture (stress failure) of pulmonary capillaries during intense exercise. Capillary rupture results from the very high pulmonary blood pressures associated with intense exercise in the horse. Most horses in training show evidence of EIPH, and the pulmonary damage caused by EIPH is cumulative.

- **Furosemide** is a safe and rapidly acting diuretic that has been used for 30 years to treat EIPH. Furosemide may reduce the intensity of EIPH but does not prevent it. Furosemide also appears to restore "normal " performance in horses that suffer from EIPH.

- **Furosemide** can "dilute out" drugs and drug metabolites in urine during peak diuresis. If the dose of furosemide is 250 mg/horse administered not less than four hours prior to post, then there is no interference with drug testing.

- **Regulatory approaches** have included the use of detention barn systems. More recently, the regulatory trend has been toward the use of plasma/serum thresholds of between 60-100 . ng/ml for furosemide.

- **Recent research** in Illinois and Canada supports recommendations that test samples be collected from the contra-lateral side from the furosemide administration. If test samples are collected from the same side as the furosemide administration, then spuriously high test sample values can occur.

- **Standard Operating Procedures (SOPS)** are required to a) protect the integrity of the test sample collection, testing procedures, and the entire split sample process, while b) allowing accurate and reproducible quantification of furosemide.

- **Specific Gravity:** The role of urine specific gravity screening in the regulation of furosemide deserves more attention. If there is no reduction in urine specific gravity, then there can be no furosemide-dependent interference with testing.

- **Ohio, Maryland and possibly others** utilize programs in which the primary screening process is for reduced urine specific gravity. Only if a) the sample's urine specific gravity is low and b) the serum threshold is exceeded is the regulatory process activated. This sequential process permits highly cost-effective regulation of furosemide.

Background

During the last year, it had become clear that there was a need for a broad review of regulatory approaches to furosemide. Regulation of furosemide began in the 1980's in response to concerns about its ability to reduce the concentration of certain drugs/metabolites in equine urine. The regulatory response was to specify a dose (250 mg/horse) and time of administration (4 hours prior to post) for furosemide to ensure that its administration did not interfere with post race urine testing.

To ensure compliance with these specifications, many jurisdictions installed detention barn systems. While effective and highly visible, these systems were also cumbersome and expensive, and the industry soon sought alternative approaches. In particular, the industry sought analytically-based approaches to regulation of furosemide usage, and these systems are increasingly used today.

These systems are based on a quantitative threshold for furosemide in post race blood. As experience with these systems developed, some jurisdictions added specific gravity testing to the protocol. More recently, it has become apparent that one needed precaution is to draw the regulatory sample from the side opposite the initial administration.

Finally, once the sample is collected, industry wide standard operating procedures (SOP's) are needed for sample handling, the handling and shipping of split samples, and the analytical methods themselves. As these methods are developed and brought into use the regulatory control of furosemide in post-race samples will become more cost effective, more user friendly, and, last but not least, will allow veterinarians to optimize the benefits of furosemide for individual horses without compromising the integrity of racing.

Given these recent advances in the art and science of the control of furosemide and the increasing dissatisfaction with the older regulatory approaches, TIP chose to bring this group together at our Spring meeting in New Orleans to review progress in this field and to point to areas in which further research is needed.

TESTING INTEGRITY PROGRAM
March 1, 1998

INTRODUCTION

Dr. Tobin: Ladies and Gentlemen, it's just after 8 a.m., actually it's closer to 8:15. We're in the Windsor Room at the River Front Hilton in New Orleans, and we're going to review furosemide and the horse. We'd like to welcome Dr. Gary Norwood to join us as a guest here today, and Dr. Ted Hill has joined us since last night. I think the rest of the group is as it was yesterday. At the American Association of Equine Practitioners meeting in Phoenix, there was considerable interest in furosemide, and I thought it would be helpful if we put a session together on furosemide. I also thought it would be useful to record it because this is a chance for us to review the field, and to write the history of the field; more importantly, to see where we need to go. So, I talked to my chair, Dr. Peter Timoney, and he approved funding to have it taped. We have a microphone here for the speaker; we have a floating mike, and if anybody wants to speak, just pass the floating mike around. We all know each other's voices, but it would probably be very helpful if you identify yourself when you speak. I will then have this tape transcribed in Lexington, and we can put together a proceedings. So, that's the rationale for the taping. Without further adieu, I'll get started.

Rick asked me to moderate the session. I'm happy to do that. First of all, I want to give a very brief overview of Exercise Induced Pulmonary Hemorrhage (EIPH) in the horse. To set the stage, I will present a lay overview, one that I presented to the Thoroughbred Owners and Breeders Association at the Breeder's Cup last fall. Dr. Harkins and I wrote this together last fall.

Exercise-Induced Pulmonary Hemorrhage: An Overview:

J.D. Harkins & Thomas Tobin, University of Kentucky

Summary

Exercise Induced Pulmonary Hemorrhage (EIPH) is caused by stress failure (rupture) of pulmonary capillaries during intense exercise. Capillary rupture occurs due to the very high pulmonary capillary pressures occurring during intense exercise; the amount of hemorrhage is a function of the exercise intensity. Each "bleeding" episode has the potential to produce pathological changes in the lungs, and these lesions tend to be cumulative and progressive. If we can prevent or reduce the adverse effects of EIPH in the horse or ameliorate them in any way, this would be a very positive thing for the health and welfare of the horse.

The Pharmacodynamics of Furosemide in the Horse:

Thomas Tobin & J. D. Harkins, University of Kentucky

Summary

Furosemide is a rapidly acting drug when administered intravenously. At 1mg/kg or less, its diuretic effect and its actions on urine specific gravity and drug detection are largely over within two hours. On the other hand, if furosemide is administered intra-muscularly, its plasma half-life is considerably longer and its effects on urinary specific gravity and drug detection are prolonged.

Based on the rapid clearance of furosemide from plasma, it was shown in the early 1980's that one way to regulate the use of furosemide was a plasma threshold of 30 ppb or greater.

The Pharmacokinetics of Furosemide in the Horse:

Dr. Rick Sams, The Ohio State University

Summary

The distribution and elimination of furosemide in the horse is reasonably well characterized and understood. Furosemide is an acidic drug, and as such is extensively bound to plasma proteins. When administered intravenously (I.V.), its plasma concentrations decline quite rapidly due to its small volume of distribution and its high plasma clearance. On the other hand, if it is administered intramuscularly, the rate of elimination is considerably slower.

Validation of the AAEP-Industry Position on Furosemide:

Dr. Rick Sams, The Ohio State University

Summary

During the late 1970's concern grew among analysts about the effects of furosemide on urinary drug detection. A study involving seven laboratories suggested that 1 mg/kg of furosemide I.V. interfered with urinary drug detection. However, in the early 1980's a second inter-laboratory study, using the AAEP recommended dose of furosemide (0.5 mg/kg @ 4 hours prior to testing), showed no significant interference with drug detection. This second study was conducted under the auspices of the American Horse Council, and it opened the way for an official industry wide position on furosemide.

Evolution of the Regulatory Control of Furosemide:

Thomas Tobin, University of Kentucky

Summary

Regulation for furosemide began in the 1980's in response to concerns about its ability to reduce the concentration of certain drugs/metabolites in equine urine. The regulatory response was to specify a dose and administration time that would not interfere with post race urine testing. To ensure compliance with these specifications, many jurisdictions installed detention barn systems. While effective and highly visible, these systems were also cumbersome and expensive, and the industry soon sought alternative approaches. More recently, the industry has sought analytically-based approaches to furosemide regulation, and these systems are now increasingly used in the regulation of this agent.

Effects of Furosemide on the Racing Performance of Horses:

Dr. Lawrence Soma, University of Pennsylvania

Summary:

1) Equine and human performance data suggest no effect of furosemide on performance in normal individuals.

2) The intensity of hemorrhage in EIPH is related to the intensity of the exercise.

3) Furosemide significantly reduces pulmonary arterial pressure, which action is consistent with its reported protective effect against EIPH.

4) Furosemide only partially protects horses against EIPH.

5) Administration of furosemide appears to bring EIPH horses back to their prior level of performance.

6) When furosemide was administered to a population of non-bleeders, the performance of a subpopulation of geldings was significantly improved.

7) The diuretic effects of furosemide are reduced by the simultaneous administration of phenylbutazone.

Regulation of Furosemide in New York:

Dr. Ted Hill, Jockey Club Steward

Summary

The Lasix program in New York was initiated in September of 1995;

Eligibility for the administration of Lasix is as follows:

A horse may qualify by any one of the following means:

- The horse has bled visibly during a race or workout, as determined by the Association Veterinarian;
- The horse has bled during a race or workout, as determined by endoscopic examination after the race or workout by an attending veterinarian;
- The horse has been qualified by the State Veterinarian or a veterinarian employed by the racetrack for the administration of Lasix in another racing jurisdiction;
- The horse has raced on Lasix in its last race in a jurisdiction with rules substantially similar to New York State.

A horse which has been eligible for the administration of Lasix may be removed from the list, upon authorization from the stewards. All certificates must be filed with the Lasix office prior to entry. Lasix shall be administered only in the following manner by an attending veterinarian who must be licensed by the New York Racing & Wagering Board:

- A single intravenous (iv) injection of no less than 250 mg (5ml) and no more than 500 mg (10 ml) during the time period from 4 to 4 ½ hours prior to the scheduled post time.

Horses are treated in their own stable without supervision. The attending veterinarian must complete and submit a Lasix tag which contains the following information:

- The date, race number, track, horse's name, trainer, dose and time of administration.

The tags are collected twice daily from designated drop sites. The Lasix coordinator reviews the information and reports any errors in administration prior to race time. Errors in time,

dose, failure to treat, or treatment of an ineligible horse will result in a late scratch. The trainer and/or veterinarian will be fined for failure to follow proper Lasix procedures necessitating a late scratch.

Regulation of the program is through submission and review of the Lasix tags and laboratory quantification. All post-race blood samples are screened for Lasix. The maximum concentration permitted is 100 ng/ml plasma.

To date, the relatively small number of overages, at the three NYRA tracks, have been addressed with interviews and warnings. Concerns with perivascular administrations and "outliers" remain a significant reason for the limited sanctions.

A uniform recommendation establishing action levels for Lasix concentration in blood and specific gravity of urine is needed to maintain the integrity of Lasix programs nationwide.

Regulation of Furosemide in Illinois and California:

Dr. Ron Jensen, Equine Medical Director, CHRB

Summary

Illinois had a typical detention barn system in which Lasix was administered to the horse in a secure area about 4 hours prior to post. More recently there has been a quantitation program in Illinois; the required dose is 150-250 mg/horse at 4 hours +/- 15 minutes prior to post. The dose is administered by a practitioner and observed by a regulator. The quantitative level is 60 ng/ml, in serum, with a graduated penalty system. Illinois does not use specific gravity data in its regulatory program.

It was early observed that post treatment test samples drawn from the Lasix injection side could yield spuriously high concentrations of furosemide if some furosemide was inadvertently administered perivascular. Based on further work on this problem and similar findings and research results in the Canadian program, test samples are now collected from the contra-lateral side from which the furosemide is administered.

Regulations Controlling the Use of Furosemide in Texas:

Dr. Allen Ray, Texas Veterinary Diagnostic Laboratory

Summary

Texas uses both a 60 ppb plasma/serum threshold and a specific gravity of less than 1.015 to regulate furosemide. If the plasma/serum threshold is exceeded, but the urine specific gravity is above 1.015, the penalty is reduced. Specific gravities are taken in the test barn, and horsemen have the option to wait for a second urine sample if they wish. Our experience in Texas

emphasizes the need for care in sample handling and standardized sample handling procedures if the split sample results are to be reproducible.

The Regulation of Furosemide: The Practitioners Perspective:

Dr. Gary Norwood, President,

American Association of Equine Practitioners

Summary

I was encouraged that some of the problems associated with Lasix quantitation, i.e. "outliers", cost, etc., are being recognized and addressed. When TIP has formulated its final recommendation, AAEP would be very interested in reviewing these guidelines for inclusion in its medication policies.

Our goal as racetrack practitioners is to provide the best veterinary health care with full use of modern therapeutic medications for the welfare of our patients. This should be accomplished within the rules of racing and without interfering with detection of illegal medications.

One particular problem facing the racetrack practitioner is a less than effective management of EIPH. AAEP has modified its recommended Lasix dosage to allow up to 1 mg/kg (10 ml) but maintaining administration at 4 hours (I.V.) prior to race. However, not all racing jurisdictions have uniformly adopted these guidelines. It is the clinical impression of many practitioners that Lasix is more effective for EIPH, 2-3 hours prior to racing.

AAEP would encourage TIP to continue research into what is the most effective dose, time of administration and route of administration of Lasix for the most effective management of EIPH without significant dilution of urine or blood and interference with testing.

Round Table Discussion and Review of Research Priorities:

All Participants

Summary

- **The regulatory trend has been towards the use of plasma/ serum thresholds of between 60-100 ng/ml for furosemide.**

- **Recent research in Illinois and Canada support recommendations that test samples be drawn from the contra-lateral side from the furosemide administration. If test samples are drawn from the same side as the furosemide administration, then spuriously high test sample readings can occur.**

- **Standard Operating Procedures (SOPS) are required to a) protect the integrity of the test sample collection, testing procedures, and the entire split sample process, while b) allowing accurate and reproducible quantification of furosemide.**

- **Specific Gravity: The role of specific gravity screening in the regulation of furosemide deserves more attention. If there is no reduction in specific gravity, then there can be no furosemide-dependent interference with testing.**

- **Ohio and Maryland utilize programs in which the primary screening process is for reduced specific gravity. Only if a) the sample specific gravity is low and b) the serum threshold is exceeded is the regulatory process activated. This sequential process permits highly cost-effective regulation of furosemide.**