THE

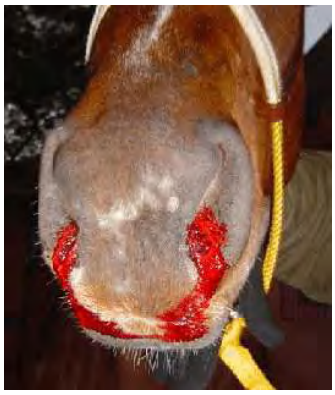
LASIX

QUESTION

Compiled by NYTHA President Richard A. Violette Jr. & the NYTHA Staff

What is exercise-induced pulmonary hemorrhage?

A horse affected by exercise-induced pulmonary hemorrhage (EIPH)--a bleeder--suffers from ruptured blood vessels in the lungs during the stress of training or competing. This physiological reaction to strenuous exercise affects not just Thoroughbred racehorses, but all equine athletes, including polo ponies, 3-day event horses, barrel racers and steeplechasers.[1] The severity of the condition is determined by the amount of blood in the horse's trachea, and graded on a scale of 0 to 4. If a horse is graded as a 4, there is blood covering the entire trachea and performance is severely affected; when the horse is in crisis, there is blood draining from one or both nostrils (epistaxis). In those cases, the condition can be critical. Some 60% of sudden deaths in racing have been attributed to pulmonary hemorrhage.[2] Studies have proven that the vast majority of race horses will suffer EIPH at some point during their careers, and that even a grade 2 can affect a horse's performance by as many as six lengths.[3]



First documented in the early 1800s, EIPH had long been suspected of having a negative impact on a racehorse's ability to perform at its peak level. But, until the early 1970s, the only symptom of EIPH beyond the subpar performance was epistaxis. That changed with the introduction of the fiberoptic endoscope more than 40 years ago, which, for the first time, allowed a veterinarian to examine the horse's upper respiratory system, and determine the origin and severity of the bleeding. Not only did this ground-breaking advance in diagnostics prove that the blood originated from the lungs, but also demonstrated that EIPH was prevalent even when epistaxis was not evident.

Dr. Ken Hinchcliff, the recognized leader in EIPH research, was lead author on studies conducted in Australia and South Africa, which proved definitively that EIPH affects the majority of Thoroughbred racehorses. The results from his Australian study, released in 2005, determined that 55% of horses suffered some level of EIPH, and was the first to clearly demonstrate the connection between EIPH and poor performance.[3] Subsequent studies have found that the prevalence of EIPH is even higher. If you scope a horse after three successive strenuous workouts, nearly 100% will be diagnosed with EIPH by the third endoscopic examination.[4]

Dr. Hinchcliff then set out to determine if the most common treatment for EIPH, the administration of Lasix, was, in fact, effective. The results of the study, conducted under racing conditions in South Africa, were published in the Journal of the American Veterinary Medical Association in July of 2009.[2] Not only was the study able to quantify the impact on performance with regard to the severity of the EIPH, but proved that Lasix was highly effective in alleviating the condition. A small percentage of the 152 horses involved in the study evidenced the highest degree of bleeding without Lasix-- grades 3 and 4--but not a single horse evidenced a grade higher than 2 after the administration of Lasix. Twice as many horses were completely unaffected by EIPH when treated with Lasix as when racing without it.

The scientific evidence is irrefutable. Horses bleed. Lasix works. But, despite this evidence, many in our industry are staunchly opposed to the use of Lasix. What are the common objections to using an effective medication to treat a condition that is at minimum uncomfortable and distressing for the horse, and, at its worst, fatal?

Separating Fact from Conjecture...

1) Racing in the U.S. survived without Lasix for hundreds of years. Why do we need it now?

• Lasix wasn't even approved for veterinary use until 1967.[5] Just a few years later came the introduction of the fiberoptic endoscope, an equine medical advancement that finally allowed the definitive diagnosis of EIPH. Anecdotal evidence that Lasix had the potential to treat EIPH led to clinical trials in the 1970s. States began permitting its therapeutic raceday use that decade.

• There have been many, many advances in medical science, in technology, in the sport of horse racing, in everyday life, that were not available 50 or 100 or 200 years ago.

- penicillin
- women are warned not to smoke or drink during pregnancy
- the internet
- football players are aggressively protected from concussion syndrome
- cell phones and tablets
- seatbelts and air bags are mandatory by law
- the starting gate
- young children must ride in car seats and wear bike helmets
- nuclear scintigraphy
- low-dose aspirin is a daily regimen to prevent heart attacks and strokes

etc, etc...

• "Because we got along without them," is no argument for not taking advantage of these advancements.

2) They race without Lasix in Europe, in Hong Kong, in Japan. Why do we need it in the U.S.?

• Outside of the United States, the majority of racing jurisdictions still use archaic medical science when it comes to an official diagnosis of EIPH.[6] If a horse does not show evidence of epistaxis (bleeding from one or both nostrils), they are not considered bleeders. With the modern technology available to aid in diagnosis, this is the medical equivalent of refusing to use an X-ray machine to diagnose fractures. It is irresponsible to wait for a horse to be in crisis to make a diagnosis.

• Outside the United States, the majority of racing jurisdictions fail to officially acknowledge the prevalence of EIPH, despite the incontrovertible evidence that it affects the majority of horses. A recent study in Hong Kong determined that 63% of the horses involved suffered EIPH after a race, and 54% suffered EIPH after a workout.[7] Lasix is prohibited in training and racing in Hong Kong, but horsemen in Europe and Australia are permitted to use Lasix during training. The trainers acknowledge its effectiveness in treating EIPH--the ONLY motivation for using Lasix during morning workouts is the alleviation of EIPH.

"Certainly, we do not want 4% of our horses to bleed from the nose, like they do in Hong Kong, when a simple, safe and effective preventative, Lasix, will prevent this severe pathological condition which requires serious medical treatment and extended rest." *Dr. Clara Fenger, DVM, Phd, TDN Op/Ed, Aug., 2014.*

• To treat EIPH, European trainers have been known to use medications other than Lasix in competition.

Nick Henderson had a positive test for the medication Tranexamic Acid in 2009 with a steeplechase horse owned by The Queen. Henderson's response to the positive test? "I was very surprised," he told *The Guardian*. "I didn't think we had administered anything terribly illegal..." He told a panel of the Royal College of Veterinary Services convened to hear the case that "plenty of trainers" were using the banned medication, and concluded, "The horse was not doped. She was given a drug for her own benefit."[8]

3) Human athletes are not allowed to compete on medication. Why would we race horses on medication?

• This is a common misconception. Amateur and professional athletes are banned from competing on certain medications--steroids, human growth hormone and illegal narcotics top the list of specifically banned substances. But there is a laundry list of medications that are permitted in competition. Quarterback Tony Romo took pain-killing injections to his ribs DURING four straight games at the beginning of the 2011 season.[9] When pro tennis player Novak Djokovic beat Rafael Nadal in the U.S. Open final that year, he was popping pain pills DURING THE MATCH.[10] Andy Murray had to call for painkillers five games into the quarter finals of the 2014 Miami Masters.[11]

• Olympic athletes, long perceived as being completely drug free, have a lengthy list of approved medications from the World Anti-Doping Agency that can be used on the day of competition, including:

That daily low-dose regimen of aspirin you take every day to prevent heart attacks and strokes? You couldn't give it to a racehorse within 96 hours of competing, or you'd end up with a positive test.

anesthetics such as novocaine, xylocaine and even adrenaline; antidepressants; antihistamines; asthma drugs; caffeine; muscle relaxers; pain relievers and anti-inflammatories; sedatives; and ulcer medications. Even cortisone injections are permitted on the day of competition. The U.S. Anti-Doping Agency grants Therapeutic Use Exemptions to athletes for any prohibited substance, including Lasix, if there are sufficient grounds for therapeutic use.[12]. (A list of WADA's approved drugs is attached).

• The medications approved for use in competition in human athletics are not nearly as tightly controlled as in Thoroughbred racing. The raceday use of Lasix is highly regulated. It must be administered no less than four hours prior to a race, in strictly controlled dosages, by a licensed veterinarian. In New York, Lasix is administered by veterinarians employed by the New York Racing Association, eliminating the practice of having a private veterinarian in a horse's stall on race day. This provision is one of the key elements of the national Uniform Medication Program.

"Virtually no member of a baseball, basketball or football team in America could pass the post-race drug testing that racehorses pass every day. In New York, more than 40% of the equine competitors are tested after each and every race. The testing standards in Thoroughbred racing are second to none." *NYTHA presentation for NY State Senate Racing Committee hearing*

• In a statement released in 2011, the Association of Racing Commissioners International revealed, "The 'anti-doping' standards in horse racing are more aggressive than those deployed in the Olympics. In fact, the worldwide annual drug testing budget of the World Anti-Doping Agency (WADA) is dwarfed considerably by the collective investment made by the state racing commissions in just one country, the United States. U.S. state racing commissions commit over $35 million annually to directly test for medication violations. By comparison, the World Anti-Doping Agency's world-wide effort relies on $26 million in funding. The financial statements published on their website reveal that, of that amount, $1.6 million is specifically earmarked for testing fees."[13]

• According to the RCI, "In 2010, 324,215 biological samples were taken and tested. Lab results show that 99.5% of those samples were found to contain no foreign or prohibited substance. In other words, only 1/2 of 1% of samples tested was found to have contained a substance in violation of the rules. An examination of racing commission data also reveals that, in those relatively rare instances when a violation of a medication rule does occur, most were associated with a legal substance administered in the normal course of equine care by a licensed veterinarian and cannot be characterized as 'horse doping' or as indicative of a 'drugging.' Those substances that could legitimately be construed as a 'horse doping' (RCI Classification Categories I and II) represent just 47 instances out of 324,215 samples tested in 2010. That represents 0.015% of all samples tested. The use of terms like 'rampant,' 'endemic,' 'widespread,' 'chemical warfare,' or 'racing's drug addiction' do the sport and the tens of thousands of families who rely on it a great disservice."[14] U.S. racing commissions sent 340,932 biological samples to professional drug testing laboratories in 2013; 99.65% of those samples were found to have no violation.[15]

"Horse racing's anti-doping program tests for more substances at deeper levels than any other professional sport. These facts are inexplicably ignored by many who wish to opine on this matter and have been successful in drawing attention to their assertions by spinning negative headlines about the sport. The perception created is not consistent with the facts."
Ed Martin, RCI "Drugs in U.S. Racing - 2010

4) Lasix is a performance-enhancing drug.

• Much has been made of the effects of weight loss on an athlete's performance. The weight loss effect of Lasix is comparable to the weight loss a horse might experience if denied hay and water for 24 to 48 hours before a race, as was often the practice before the advent of Lasix. While Lasix use is strictly controlled, there is no oversight for if or when a trainer takes away a horse's nutrients. Will this necessitate the introduction of security to ensure that all trainers observe the same protocol? Will it lead to headlines proclaiming, "Horses Starved and Dehydrated Before They Race"?

The weight loss effect of Lasix mirrors what a horse might experience if denied hay and water for 24 to 48 hours before a race. Is taking away a horse's hay and water for even a half day humane?

• Lasix does not allow a horse to perform beyond its peak natural ability. It alleviates, but does not eliminate, a condition that hampers peak performance. Anecdotally, historically and scientifically, it has been demonstrated clearly that EIPH adversely affects performance. Horses run slower when they bleed. Anecdotally, historically and scientifically, it has been demonstrated clearly that Lasix is significantly effective in minimizing EIPH. The refusal to connect these dots is the height of, "Don't confuse us with the facts."

> **"No amount of Lasix will make a horse run past his ability."**[28] *Dr. Scott Palmer, equine medical director for New York State and past president of the AAEP*

• Even those who once had been staunchly opposed to Lasix have recognized that it is a performance restorer, not an enhancer. A 1988 *Washington Post* article entitled, "Handlers Hope Lasix Will Help Private Terms Regain Lost Form," documented how GI Wood Memorial winner Private Terms' form deteriorated due to EIPH, then was restored when he was put on a Lasix regimen. According to the article, trainer Charlie Hadry, "reiterated his belief that the use of Lasix in no way diminishes Private Terms' status as a racehorse of high quality. It's not a stimulant, Hadry said, but a drug that rids the body of surplus fluids and simply will allow Private Terms to run to his potential." Then 80, the late Stuart Janney Jr., owner/breeder of Private Terms, and of the great Ruffian, was quoted in the article, saying, "I know I was very much opposed to using Lasix or anything else at one time. But I've had [bleeding] happen so many times to so many of my horses that I don't feel that way any more. I've gotten to be an old man, and I even have to take Lasix once in a while."[16]

5) Why is there such widespread use of Lasix?

• There is a cumulative effect that can increase the severity of EIPH each time it occurs. An analogy would be metal fatigue in airplane wings. The airplane is subject to ongoing stress that creates tiny fractures in the wings. Over time, as the stress continues, the fractures worsen, and can lead to catastrophic failure. "In the long term, reducing the severity of bouts of EIPH is beneficial to the health of the horse's lungs. The presence of blood in them has been shown to induce permanent changes in their tissue structure," then-AAEP President Dr. Robert D. Lewis stated in a 1995 press release.[17]

> **"People who are advocating the elimination of [Lasix] have to explain why they want to deny a horse medicine that has been shown to be beneficial to the horse's health and well-being."** [29] *Michael Davis, physiological sciences professor and Oxle Endowed Chair in Equine Sports Medicine at Oklahoma State University's Center for Veterinary Health Sciences.*

• Anthony Verderosa, Chief Examining Veterinarian for the New York Racing Association (NYRA), reported that episodes of epistaxis, the most severe form of EIPH--when a horse is in crisis and bleeding from the nostrils--was IMMEDIATELY reduced nearly 80% in New York after Lasix was legalized in the state in 1995, and has remained at the lower level in the two decades since.[27]

• Speaking during the "International Summit on Race Day Medication, EIPH and the Racehorse" in 2011,

Graham Motion and Christophe Clement, two of the four trainers invited to speak, voiced the opinion that it is necessary to be proactive in the prophylactic treatment of EIPH. "I certainly breeze some of the 2-year-olds on Lasix, even if they haven't been bleeding previously," said Motion, who has not had a single positive test since taking out his trainer's license in 1993. "Prevention is important--I don't want them to start bleeding that early." Clement, who also boasts a pristine record, remarked, "If a horse bleeds, right away, you've got a situation. You've got to do everything you can. You can't avoid bleeding--it's a fact of life. What you can avoid is it becoming chronic." It should be noted that both Motion and Clement are originally from Europe.[18]

• Proper maintenance of EIPH is key to maintaining the health of the equine respiratory system, and is in the best interest of the horse.

6) Does Lasix mask other medications?

• During the "International Summit on Race Day Medication, EIPH and the Racehorse," Dr. Richard Sams, PhD, director of HFL Sport Science Inc. in Lexington, stated that, after the American Association of Equine Practitioners came up with a universally accepted standard of practice for Lasix in 1983--recommending that it be administered intravenously and at a time four hours prior to a race--the concern that Lasix could affect the detectability of other medications was addressed. "That concern is largely eliminated when [Lasix] is administered in a tightly controlled environment, as it is in the United States," Dr. Sams said. He concluded, "I don't refer to [Lasix] as a masking agent. It's impact on post-race testing is not very significant."[18]

> **"Furosemide does not interfere with drug detection, provided that it is administered at least four hours prior to racing and within an intravenous dose range of 250 to 500 mgs. New, ultra-sensitive instrumental testing, combined with the regulatory control outlined above, precludes the possibility of furosemide interference with drug testing."** *Dr. George Maylin, director of the New York State Racing and Wagering Board's Equine Drug Testing Program at Morrisville State College*.

• In an article in *Daily Racing Form*, Steven Crist said, "The whole issue of whether Lasix can mask other drugs was a valid concern a generation ago--perhaps the best reason to oppose its use--but from all veterinary accounts this is now a non-issue. The vastly increased precision of testing, and a greater reliance on plasma rather than urine tests, has made this a moot point."[19]

7) Does the use of Lasix contribute to fewer starts per horse per year? Will it weaken the breed?

• The average number of annual starts per horse has dropped dramatically in the U.S., from a peak of 11.31 starts per year in 1960 to a low of 6.06 starts per year in 2010. But the trend started before the advent of Lasix, with the average dropping to 10.23 by 1975. When the AAEP standard for Lasix administration was approved, the average was down to 8.28 annual starts, but it held relatively steady for the next decade, with the average at 7.84 starts in 1994. There is no anecdotal or scientific evidence to single out Lasix as the cause for the decline, and the numbers have actually rebounded slightly since 2010, with the average at 6.3 starts in 2013.[20]

• There is a misconception that horses in countries that do not allow the raceday use of Lasix average more starts per year than those in the U.S. In fact, the average in Europe is no better than in the U.S., and in some countries, it is considerably lower. Horses in Germany, lauded for its high standards, average 5.0 starts a year; in France, 6.0; in England, 6.0; in Italy, 5.2. Australia's average is similar to the U.S. at 6.2 annual starts; New Zealand averages 5.8 starts a year.[21]

• Countering arguments that American horses are weaker than their foreign counterparts, Dr. Hiram Polk Jr. presented, "Case Study: North American Pedigrees Down Under," during the 2013 Jockey Club Round Table, and demonstrated that horses with North American bloodlines raced more frequently and needed less time between races than those with Australian pedigrees.[22]

• There are many potential contributing factors to the decrease in the number of starts. The '80s saw the demise of "Millionaire's Row," the area of the Belmont Park backstretch where the old (and wealthy) names in racing once stabled their horses. The stalls had been filled with the Rokeby and Greentree and Calumet and Darby Dan horses, horses bred from meticulously selected bloodlines that prized soundness. As the venerable family stables cut back or disappeared completely, the explosion of the commercial breeding industry was underway, and the standards of the breeding industry changed. An emphasis was placed on precocious speed with less regard for soundness. Stallions went to the breeding shed after making just a handful of starts because there was so much money to be made in stud fees. Foal surgeries to correct conformational flaws became common-place and acceptable. Young horses, formerly turned out and toughened in very natural conditions, were suddenly being raised like hothouse flowers. All of these factors could contribute to raising softer horses that don't race as often.

• Another potential factor in the decrease in the number of annual starts is the fact that a premium is placed on a trainer's winning average. The late Hall of Famer Bobby Frankel, who was known to scratch his horses if the conditions did not appear favorable for a victory, was hired by Juddmonte Farm based, in part, on a computer analysis that highlighted his exemplary win percentage.[23] A 10% strike rate is a knock against a trainer. The acceptance of the "bounce" theory, quantifying the negative effect that a peak effort can have on a horse's next start, has also tempered trainers' enthusiasm for running back on less than a month's rest.

8) The public is anti-Lasix.

• There has yet to be a published survey that directly addresses the Lasix issue. The survey questions posed are ambiguous, generic and, at times, leading. The results are much what you would expect if you asked the public, "Do you think kids should take drugs?" when trying to determine if there was support for medicating asthmatic children.

• In an Op/Ed for the *Thoroughbred Daily News* in October of 2014, professional handicapper Jerry Brown

stated that those in his profession supported the continued use of raceday Lasix, and added, "...the Lasix issue is being lumped in with the illegal drug issue, because both involve drugs, and in some cases because people have agendas. I've been heavily involved in trying to stop cheating in our game for a long time, not for idealistic reasons, but because money is being stolen from honest horsemen and horseplayers [like yours truly]. Attempting to stop something illegal, which everyone agrees about, and attaching it to banning a legal therapeutic drug, which is controversial, is like having a bill to fix the Veterans Administration, and combining it with declaring war on Iran, because both involve the army."[24]

• Attempts have been made to show a correlation between the raceday use of Lasix and the issue of steroids in professional sports. The fact is, when the call came to ban steroids in Thoroughbred racing, the response was a unified stand to phase out the medication as quickly as possible. In stark contrast to the Lasix issue, horsemen supported the elimination of steroid use, because there was no single therapeutic application for steroids. There is a single scientifically supported use for Lasix. Horses bleed. Lasix works.

• During a presentation of the McKinsey Report during The Jockey Club's 2011 Round Table Conference on Matters Pertaining to Racing, a pie chart purporting to support the conjecture that the public is anti-Lasix demonstrated that 74.5% of those who responded to a survey of members of the Horseplayers Association of North America were for the elimination of raceday medication. In fact, according to the HANA website, the question posed was, "Do you support The Jockey Club's position on raceday medication." Responders had to click on a link to the TJC position; it was not posted with the survey. The question was clearly slanted; no clear-minded individual could in any way interpret this survey as an objective attempt to find the truth about the Lasix issue. An earlier survey of HANA members, conducted in 2009, found that only 59% were "extremely" concerned over the ILLEGAL use of medication and drugs. That means 41% did not consider illegal medication a major concern.[25] Go figure.

"We know from a scientific and a medical perspective that furosemide is good for horses that race, but is it good for the business of racing? That paradox is one we've made an enormous effort to try to resolve. Fundamentally, we believe what's good for the horse has to be good for racing."[30] *Dr. Scott Palmer, equine medical director for New York State and past president of the AAEP*

• Despite the depth and breadth of the McKinsey Report presented at the Round Table, the published results did not include any specific reference to Lasix in any of the polls of the public, racing fans and industry stakeholders. "Medication of horses" was considered a significant issue by 78% of stakeholders interviews, but only 25% felt that medication issues "adversely impacted wagering."[26]

• In a 2011 survey of racing fans included in the McKinsey Report, only 36% felt that "medication was one of the top three issues facing racing." But 78% "would stop betting if they knew horses were not treated well."[26] One could easily argue that banning Lasix, a medication that safely and effectively treats a condition suffered by the majority of racehorses, could be defined as not treating the horse well. After Lasix was permitted for raceday use in New York 16 years ago, the incidence of epistaxis following a race immediately dropped nearly 80%.[26] How do you explain to racing's fans a willingness to let 80% more horses suffer critical bleeding from the nostrils after they run, and put them at risk for a condition that, when severe enough to cause epistaxis, can be fatal?

• In a *Daily Racing Form* article headlined, "Banning Lasix Won't Stop the Bleeding," Steven Crist said, "If you poll civilians about whether racing [or water polo, or your local crafts fair] would be better off without 'performance-enhancing drugs,' they will answer in the affirmative. From personal experience, however, I see no evidence that this translates to Lasix keeping anyone away from racing. Over the last decade, I have conducted over 100 question-and-answer seminars with tens of thousands of fans and players at tracks and betting parlors across the country. The next one I meet who thinks Lasix is a major issue, or a reason not to play the races, will be the first."[18]

THE REAL ISSUE...

Those opposed to the use of Lasix trumpet they are concerned, first and foremost, with the welfare of the horse. But the arguments offered against the use of Lasix never address what is in the best interest of the horse. Opponents are concerned about what the international racing community thinks, what the public thinks, the long-term effect on the breed, testing standards, etc. There isn't a single argument that stresses the health and welfare of the horse.

The majority of horses bleed when under exercise-induced stress. It is result of their physiology. EIPH affects performance horses of all breeds. It is a condition that is at minimum uncomfortable and distressing for the horse, and, at maximum, fatal. The only way to eliminate EIPH completely is to shut down the racetracks and put all the horses out to pasture. That is not an option.

If there was a viable alternative to Lasix, the industry would embrace it. But opponents have no researched and reasoned plan for dealing with EIPH in the future. The thinking seems to be, "eliminate Lasix and somehow the horses will stop bleeding." That's not going to happen. There is a problem, and ignoring it isn't the solution.

We do have a safe, effective treatment that allows horses to perform, not over and above their natural ability, but to the highest level their natural talent dictates. Until a better option is discovered, it is unarguably in the best interest of the horse--and, by extension, in the best interest of the sport and the industry--to alleviate EIPH with Lasix.

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RACING COMMISSIONERS INTERNATIONAL

Press Release

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Contact: Ed Martin (859) 224-7070

RCI: Racing's Drug "Problem" Overstated

Lexington, KY - "With very few exceptions, almost all race horses tested for drugs are found to be clean, a fact that undermines the credibility of those who peddle the perception that racing has an out of control drug problem," RCI President Ed Martin said today in releasing an RCI report entitled **Drugs in Racing 2010 - The Facts** *(available here).*

In 2010 US racing regulators sent 324,215 biological samples to a network of professional testing labs that utilized standards more stringent than those used for the Olympics. More than 99.5% of those samples were found to be clean.

"Despite the fact that racing regulators test for more substances with greater sensitivity than any other sport, less than one half of one percent of all tests detected a substance not allowed to be in the horse on raceday," he said.

The RCI report also shows that instances of "horse doping" are rare, representing 0.015% of all samples tested. The ten-year trend for findings that might be characterized as "doping" has remained flat, while there has been a decline during the past decade in the number of therapeutic overages that have resulted in regulatory action. Total medication actions in 2010 were 20% less than 2001, although RCI noted it was not prepared to describe it as a trend.

"Racing, like other sports, has a drug challenge," Martin said, "We cannot lessen our efforts because there are a relative few who will attempt to circumvent the rules for their own purposes. Our commissions, labs, and research centers need adequate resources if we are to remain current and prepared as new substances emerge and find their way to the backstretch."

Martin contends that the reality of the drug testing program is often misunderstood and mischaracterized.

The RCI report notes that equine care has evolved to be more medication-reliant in the same way human care has. Racing commission data shows that in those rare instances when a violation of a medication rule does occur, most were associated with a legal substance administered in the normal course of equine care by a licensed veterinarian and cannot be characterized as "horse doping" or as indicative of a "drugging".

Note: To access the report **Drugs in Racing 2010 - The Facts**, please click here.

#######

1510 Newtown Pike, Lexington, Kentucky 40511
(859) 224-7070

DRUGS IN U.S. RACING - 2010

THE FACTS

With more rigorous standards than the Olympics, professional horse racing has the most aggressive drug testing program in professional sports, testing for more substances with greater sensitivity than anyone else.

September 1, 2011

1510 Newtown Pike, Lexington, Kentucky 40510 • telephone: 859 224 7070 • www.arci.com

Summary:

- Horse racing is subjected to the most aggressive drug testing program of any professional sport, testing for more substances with greater sensitivity;
- 324,215 biological samples taken from racing horses were submitted to testing labs in 2010;
- Less than one half of one percent (.493%) of those tested samples were found to contain a substance not allowed by racing's medication rules;
- Of those, 94% were overages of legal therapeutic medications at concentrations in excess of permitted levels. These medications are used routinely in equine care by licensed veterinarians and cannot be equated with "horse doping";
- Only 47 of the over 320,000 samples tested in 2010 contained a Class 1 or Class 2 [1] substance that could qualify for the term "horse doping".
- Possible "Horse doping" accounted for 0.015% of total samples tested. Such instances have remained rare for the past ten years despite dramatic increases in testing sensitivity.
- Overall violations of the medication rules in 2010 were 20% less than 2001.
- The $35 million collective investment by the US state racing commissions on drug testing dwarfs the entire $26 million budget for the World Anti-Doping Agency.
- Claims that illegal drugs are "rampant", "endemic", "widespread" in horse racing are not consistent with the facts, although illegal drug use does exist and there is an ongoing need to support efforts to detect and punish those responsible.

[1] See Classification definitions later in this document.

Narrative:

On May 5, 2011, the front page of USA Today was headlined "Chemical Warfare in Horse Racing Targeted". The article was prompted by the comments of a prominent public official who declared that "Chemical warfare is rampant on American racetracks". Such salacious comments create an undeserved negative perception of a sport that is responsible for the employment of over 380,000 people across the country.

There has been much written or claimed about the extent to which professional horse racing has a drug problem. Surely there is a challenge as equine care has evolved to be more medication reliant in the same way human care has. Today, legal medications are often prescribed by physicians and veterinarians to improve the health and quality of life for people and animals.

This conventional reliance on legal medication presents a challenge for racing regulators who must ensure compliance with the rules protecting the public and the horse. Many who have been widely quoted on this issue have not had access to the data contained in this report. This data, obtained from state regulatory bodies, represents an unbiased view of the extent to which drug violations actually occur in the sport.

It has long been acknowledged that professional horse racing - thoroughbred, standardbred, and quarter horse contests - are aggressively regulated by the states because pari-mutuel wagering on the outcome of these contests has been an authorized and limited form of gambling originally intended to support rural and agricultural economies.

The "anti-doping" standards in horse racing are more aggressive than those deployed in the Olympics. In fact, the worldwide annual drug testing budget of the World Anti-Doping Agency (WADA) is dwarfed considerably by the collective investment made by the state racing commissions in just one country, the United States. U.S. state racing commissions commit over $35 million annually to directly test for medication violations. By comparison, the World Anti-Doping Agency's world-wide effort relies on $26 million in funding. The financial statements published on their website reveal that of that amount, $1.6 million is specifically earmarked for testing fees.

Horse racing's anti-doping program tests for more substances at deeper levels than any other professional sport. These facts are inexplicably ignored by many who wish to opine on this matter and have been successful in drawing attention to their assertions by spinning negative headlines about the sport.

The perception created is not consistent with the facts.

In 2010, 324,215 biological samples were taken and tested.[2] Lab results show that 99.51% of those samples were found to contain no foreign or prohibited substance. In other words only less than one half of one percent of all samples tested was found to have contained a substance in violation of the rules[3].

An examination of racing commission data also reveals that in those relatively rare instances when a violation of a medication rule does occur, most were associated with a legal substance administered in the normal course of equine care by a licensed veterinarian and cannot be characterized as "horse doping" or as indicative of a "drugging".

Those substances that could legitimately be construed as a "horse doping"[4] (RCI Classification Categories I and II) represent just 47 instances out of 324,215 samples tested in 2010. That is less than two one hundredths of one percent (0.015%). The use of terms like "rampant", "endemic", "widespread", "chemical warfare", or "racing's drug addiction" do the sport and the tens of thousands of families who rely on it a great disservice.

For testing, racing commissions retain professional laboratories who are subject to commission oversight as well as quality assurance programs. In addition, laboratory findings are subject to review by an independent reference laboratory as well as adjudicatory appeal. In 2010, as in previous years, we are not aware of any laboratory finding that was determined to be invalid.

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[2] Thirty-two US racing regulatory jurisdictions responded to the association's survey.

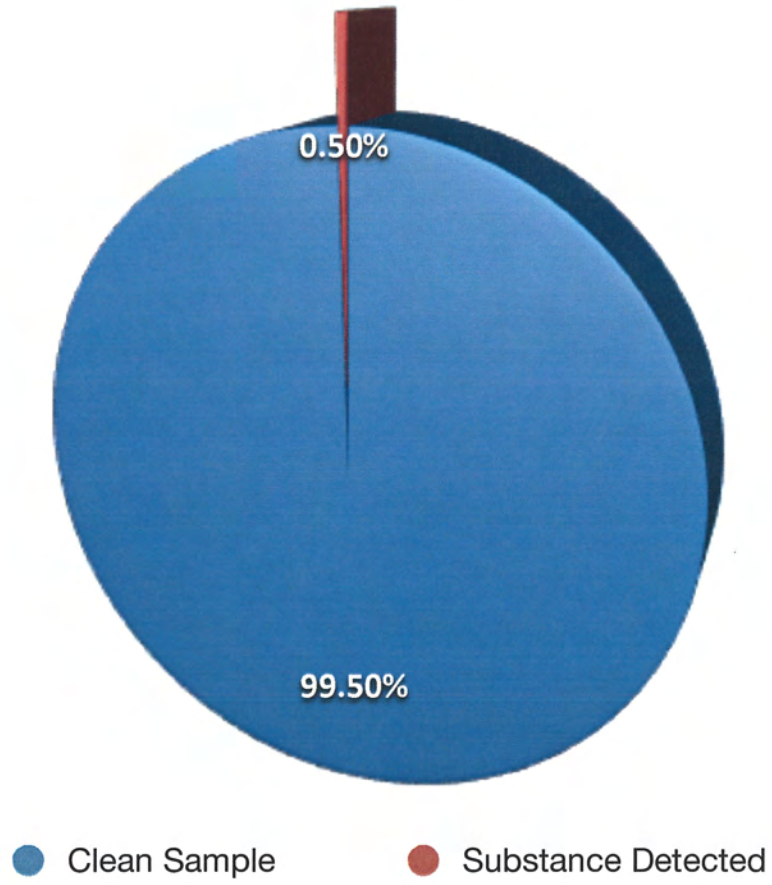
[3] In many cases actual violations are determined based on the testing result of a plasma and urine sample. Violations noted in this report are equine related.

[4] Some Class 2 positives can be for therapeutic drugs that could be a medication error and not qualify as a "doping"; Some Class 1 positives are unintentional secondary contaminations; some positives are associated with human drug abuse and due to the sensitivity of the testing substances are detected in horses these individuals have come in contact with.

2010 Samples Tested and Results:

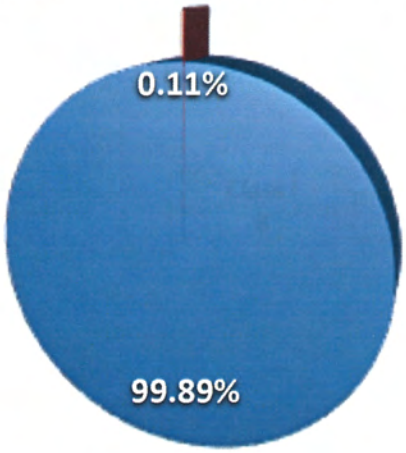
Jurisdiction	Samples Tested	Substance Detected	%
Arizona	1,457	37	2.54%
Arkansas	1,146	7	0.61%
California	40,470	101	0.25%
Colorado	491	9	1.83%
Delaware Harness	7,504	9	0.12%
Delaware Thoroughbred	2,544	12	0.47%
Florida	16,155	135	0.84%
Illinois	14,071	60	0.43%
Indiana	8,719	20	0.23%
Iowa	3,540	9	0.25%
Kentucky	10,851	81	0.75%
Louisiana	12,880	80	0.62%
Maine	3,313	5	0.15%
Maryland	5,098	29	0.57%
Massachusetts	3,420	13	0.38%
Michigan	2,738	51	1.86%
Minnesota	3,989	130	3.26%
Montana	224	5	2.23%
Nebraska	3,094	47	1.52%
New Jersey	39,196	31	0.08%
New Mexico	8,986	56	0.62%
New York	52,748	60	0.11%
North Dakota	71	5	7.04%
Ohio	16,445	170	1.03%
Oklahoma	9,623	51	0.53%
Oregon	1,965	18	0.92%
Pennsylvania	37,114	217	0.58%
South Dakota	100	0	0.00%
Texas	8,769	66	0.75%
Virginia	1,432	8	0.56%
Washington	608	3	0.49%
West Virginia	5,454	75	1.38%
All US Jurisdictions:	324,215	1600	0.4935%

2010 Nationwide in the United States:

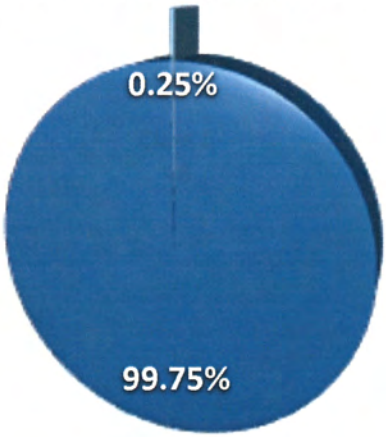


2010 Top Four Racing States:

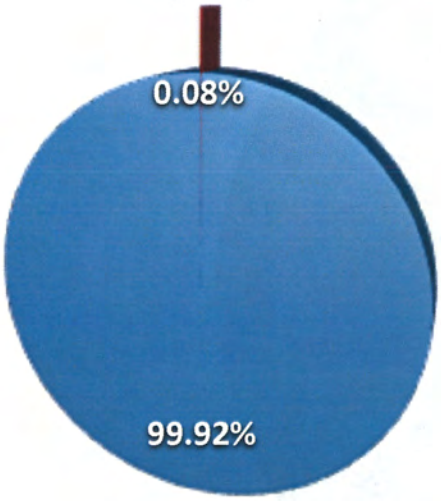
New York: 52,748 tests



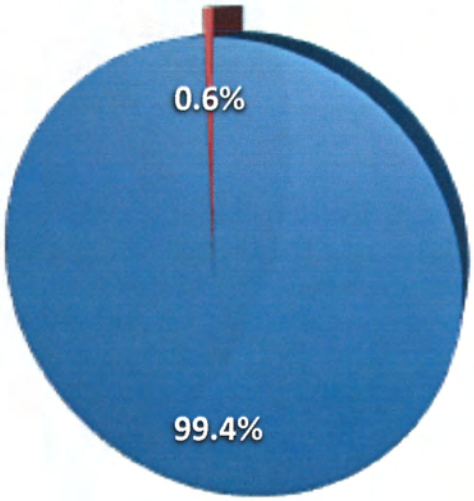
California: 40,470 tests



New Jersey: 39,196 tests

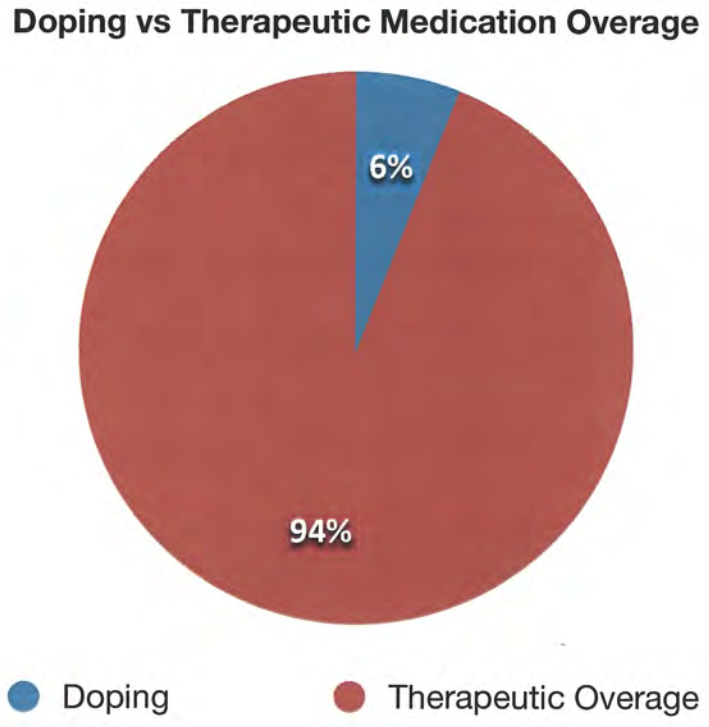


Pennsylvania: 37,114 tests



Doping vs. Overage:

Considering that Class I and Class II violations can best be described as "doping"[5] and others characterized as therapeutic overages of legal substances the following chart should put the results of the drug testing program in proper context. Again, it is important to note that the doping rate is 0.015% of all samples tested, an extremely rare occurrence. Ninety-four percent of the horses found to be in violation of the medication rules in 2010 were cited for a substance with less capacity to affect performance than those that would qualify as doping agents. Of those, 72% are for violations of Class IV substances with even less potential to affect performance, if at all.

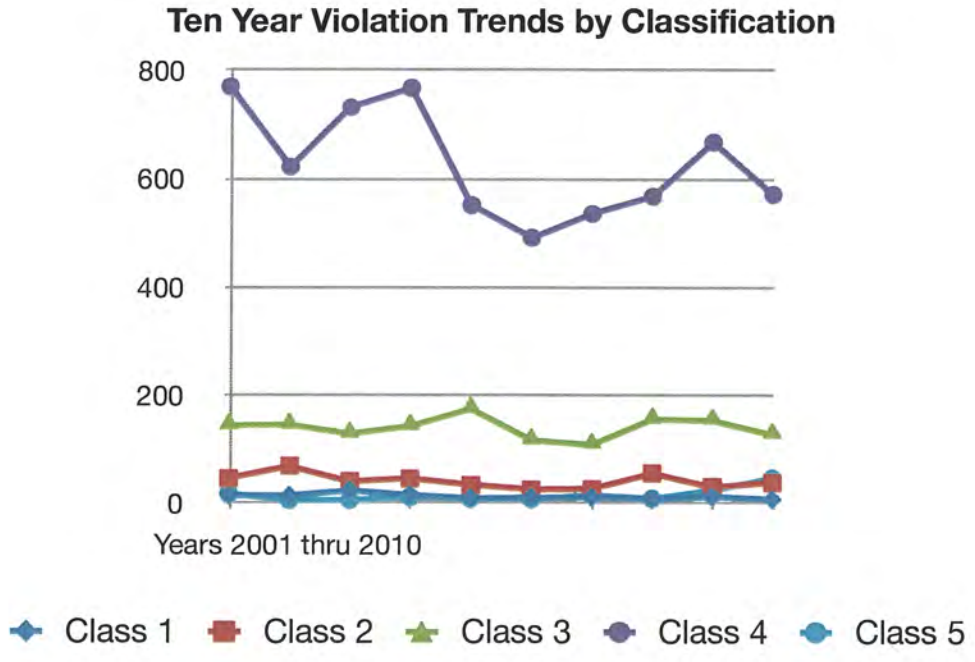


[5] The applicability of this term to a specific case depends totally on the facts presented in that case. This term is used as a general characterization and may not be applicable to all violations found in this category as noted in Footnote 4.

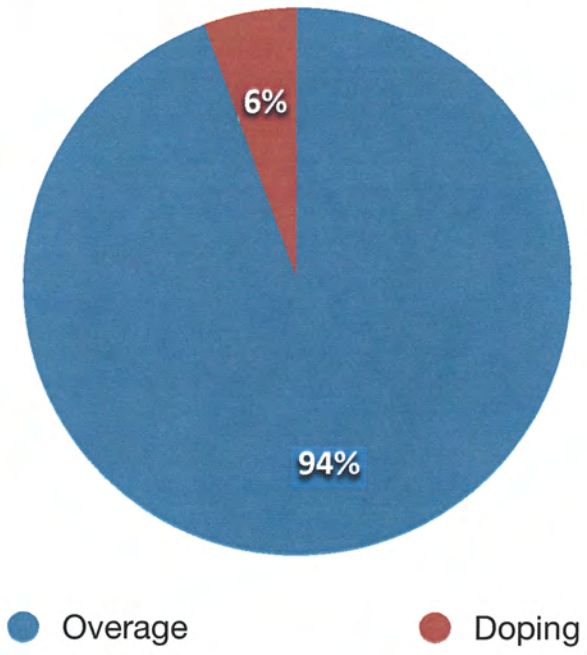
Trends:

An analysis of the data from 2001 through 2010 reveals no prevailing pattern concerning the number or severity of violations of racing medication and doping rules. Violations remain relatively rare and this has remained constant over the past decade. It is important to note that total medication rule violations in 2010 were 20% less than the 2001 violations.

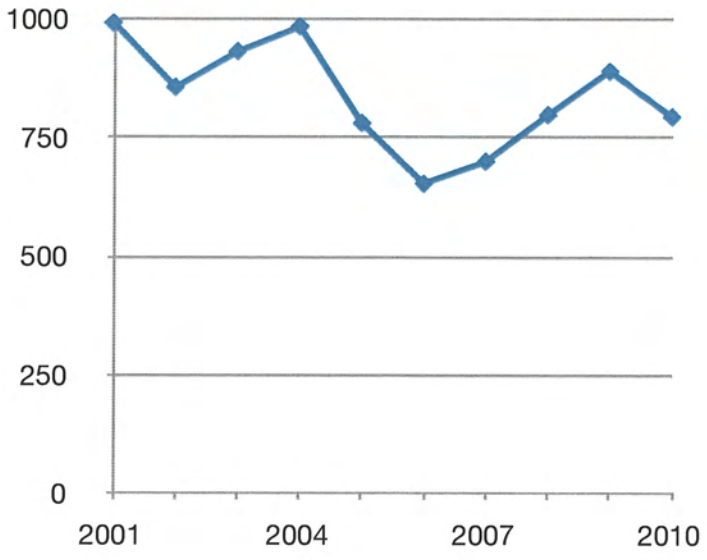
	Class 1	Class 2	Class 3	Class 4	Class 5
2001	14	46	144	770	18
2002	15	69	145	622	6
2003	24	41	129	732	6
2004	16	46	143	768	12
2005	10	34	175	552	10
2006	11	26	117	492	8
2007	12	27	109	536	16
2008	9	56	156	568	10
2009	13	31	154	668	25
2010	8	39	128	572	48



10 Year Doping vs. Therapeutic Medication Overage



10 Year Total Violations



Furosemide:

The United States is one of several nations where the raceday use of the diuretic furosemide is permitted. This medication, used to reduce instances of exercise induced pulmonary hemorrhage (EIPH), is allowed under strict conditions requiring administration no less than four hours prior to the race. For the purpose of this report we handled violations of the furosemide rule separately as a trainer can be cited for not having the medication in his horse as well as for an overage. Furosemide violations should not be considered "horse doping".

Use of furosemide is disclosed to the public in the racing program and while there is an ability to affect performance in some - but not all - horses, the public policy is not restrictive in allowing veterinarians to qualify a horse to receive this treatment based on the detection of minor levels of EIPH.

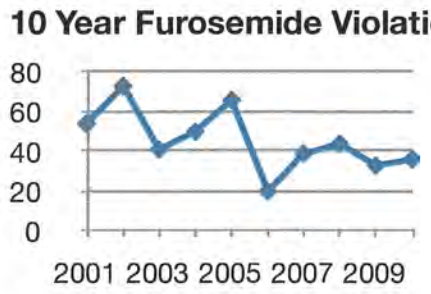
Since most horses race with furosemide it is a disservice to the sport to contend that one horse has an unfair advantage over another in a particular contest.

EIPH is the only equine condition that has warranted an exception to permit a prophylactic treatment on race day with medication. It is wrong to equate the use of this medication to paint a picture that racing is "drug ridden".

In 2010 there were 36 violations of the furosemide rules out of 324,215 samples tested.

The 2010 instances of furosemide violations are 33% less than in 2001. The trend has been generally downward. It is important to remember, as with all statistics in this report, that the instances of a violation of racing medication rules are not a frequent occurrence, representing one half of one percent of all samples tested.

2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
54	73	41	50	66	20	39	44	33	36



Drug Testing Challenges:

The statistics in this report should not be interpreted to say that there are not challenges facing horse racing's drug testing program. New substances are developed each year and there are individuals willing to use them on a horse in an attempt to enhance performance or cheat. Those who administer substances that would never be condoned by a licensed veterinarian must be caught and properly sanctioned. To do this investments in research and investigations are essential if racing's drug testing program is to remain as strong as it is today.

State budget constraints are putting pressure on commission resources and can limit the amount of research and intelligence gathering activities that are possible. This challenge has been met, in part, by the racing industry through its investment in the Racing Medication and Testing Consortium and the tracks specifically through their continued investment in the Thoroughbred Racing Protective Bureau (TRPB). The U.S. Jockey Club has made considerable investment in projects to enhance integrity, support commissions, and better protect the welfare of the sport's equine athletes. The National Thoroughbred Racing Association's Safety and Integrity Alliance also makes a positive commitment to racing integrity through its investment in race track accreditation.

These efforts do not mitigate the need to ensure that racing commissions have adequate resources available to maintain an expansive and effective drug testing program that can evolve as scientific advances are made in both testing technology and equine care.

Disclaimer:

The statistics contained in this report were provided to the Association of Racing Commissioners International (RCI) directly by individual state racing commissions through their management and submission of violation data contained in the RCI database or in response to specific requests form RCI staff. In some cases, information has been obtained indirectly through published annual reports. Questions concerning specific jurisdictions should be directed to that jurisdiction. No statement in this report is intended to be indicative of a specific motive or lack thereof of any individual who is alleged to have violated a racing medication rule. Statements made in this report are designed to make a general assessment as to the extent of drug violations in professional horse racing. Information requests on specific violations or individuals should be directed to the appropriate regulatory entity. RCI is a not-for-profit 501(c)(6) providing services and information to government racing regulators. RCI is not liable for any errors contained in this report which has relied on information obtained from third party state racing commissions.

Classification Definitions

- **Class 1**: Stimulant and depressant drugs that have the highest potential to affect performance and that have no generally accepted medical use in the racing horse. Many of these agents are Drug Enforcement Agency (DEA) schedule II substances. These include the following drugs and their metabolites: Opiates, opium derivatives, synthetic opioids and psychoactive drugs, amphetamines and amphetamine-like drugs as well as related drugs, including but not limited to apomorphine, nikethamide, mazindol, pemoline, and pentylenetetrazol. Though not used as therapeutic agents, all DEA Schedule 1 agents are included in Class 1 because they are potent stimulant or depressant substances with psychotropic and often habituative actions.

- **Class 2**: Drugs that have a high potential to affect performance, but less of a potential than drugs in Class 1. These drugs are 1) not generally accepted as therapeutic agents in racing horses, or 2) they are therapeutic agents that have a high potential for abuse. Drugs in this class include: psychotropic drugs, certain nervous system and cardiovascular system stimulants, depressants, and neuromuscular blocking agents. Injectable local anesthetics are included in this class because of their high potential for abuse as nerve blocking agents.

- **Class 3**: Drugs that may or may not have generally accepted medical use in the racing horse, but the pharmacology of which suggests less potential to affect performance than drugs in Class 2. Drugs in this class include bronchodilators, anabolic steroids and other drugs with primary effects on the autonomic nervous system, procaine, antihistamines with sedative properties and the high-ceiling diuretics.

- **Class 4**: This class includes therapeutic medications that would be expected to have less potential to affect performance than those in Class 3. Drugs in this class includes less potent diuretics; corticosteroids; antihistamines and skeletal muscle relaxants without prominent central nervous system (CNS) effects; expectorants and mucolytics; hemostatics; cardiac glycosides and anti-arrhythmics; topical anesthetics; antidiarrheals and mild analgesics. This class also includes the non-steroidal anti-inflammatory drugs (NSAIDs), at concentrations greater than established limits.

- **Class 5**: This class includes those therapeutic medications for which concentration limits have been established by the racing jurisdictions as well as certain miscellaneous agents and other medications as determined by the regulatory bodies. Included specifically are agents that have very localized actions only, such as anti-ulcer drugs, and certain anti-allergic drugs. The anticoagulant drugs are also included.

South African Lasix Study

Study: Furosemide Has Health Benefits for Thoroughbred Racehorses

Schaumburg, IL

A groundbreaking study to be published in the *Journal of the American Veterinary Medical Association (JAVMA)* shows that furosemide does more than enhance performance in Thoroughbred racehorses; it also has beneficial effects on the health and welfare of those horses.

Most countries ban the race-day use of furosemide because it improves performance in racehorses. Only the United States, some South American countries, including Brazil, and some tracks in Canada, allow the use of furosemide on race day.

"The data in the study provides the most reliable information to guide the highly politicized debate over use of furosemide in horses," says Dr. Kenneth Hinchcliff, professor and dean of the Faculty of Veterinary Science, The University of Melbourne, and co-author with Professor Paul Morley, Colorado State University, and Professor Alan Guthrie, University of Pretoria in South Africa. "To date, there has been only a limited amount of high-quality evidence - and none matching the quality of this study - to inform the debate. We know that furosemide is associated with improved performance, and that exercise-induced pulmonary hemorrhage (EIPH) markedly affects race performance. But we didn't know the answer to the third - and most important - leg of the trifecta: Whether furosemide is effective in treating EIPH. We now know."

The study, "Efficacy of furosemide for prevention of exercise-induced pulmonary hemorrhage in Thoroughbred racehorses," which will appear in the July 1, 2009, issue of the *JAVMA*, is the first of its kind to draw a definitive link between the use of the drug and the prevention of the bleeding condition in Thoroughbreds.

The study included 167 Thoroughbred racehorses that performed under typical racing conditions in South Africa between Nov. 20 and Nov. 28, 2007. Each horse in the study raced twice, once after receiving furosemide before the race and once after receiving a placebo. The results showed that horses were 3 to 11 times as likely to have EIPH after placebo administration as they were after administration of furosemide. In addition, about two-thirds of the horses that had EIPH after administration of the placebo had a reduction in EIPH severity when treated with furosemide.

Hinchcliff, Morley and Guthrie conducted what is considered the "gold standard" of scientific studies, performing a well-designed, randomized, controlled clinical trial.

The study was truly an international collaboration.

"The study could not have been conducted without the strong support of the racing industry, both through the Grayson-Jockey Club Research Foundation and Racing Medication and Testing Consortium in the United States, and the racing industry in South Africa," said Guthrie.

"This study design is similar to those used to test the efficacy of treatment in human medicine," Morley said. "To date, such studies have been uncommon in veterinary science, and we believe that our study is unique among studies of drug efficacy in racehorses under conditions of racing. The rigorous approach to study design resulted in a very clear result."

Once the study results are widely circulated, the authors anticipate that some racing jurisdictions may reconsider their ban on the use of furosemide.

"It is likely that racing jurisdictions will reconsider, in one way or another, their position on the use of furosemide," they said. "However, the decision to allow or disallow the use is based on the balance of a number of factors, and resolution of this complex situation will take some time."

"The challenge will now be for countries such as England, Hong Kong, Australia and South Africa that do not currently permit race-day use of furosemide. The challenge that they will face is balancing the animal-welfare aspect of being able to prevent or reduce the condition against the imperatives for drug-free racing. Additionally, instituting race-day administration of furosemide would be a significant added expense to racing."

For a copy of the study, contact David Kirkpatrick at 847-285-6782 or dkirkpatrick@avma.org

The AVMA and its more than 78,000 member veterinarians are engaged in a wide variety of activities dedicated to advancing the science and art of animal, human and public health.

Efficacy of furosemide for prevention of exercise-induced pulmonary hemorrhage in Thoroughbred racehorses

Kenneth W. Hinchcliff, BVSc, PhD, DACVIM; Paul S. Morley, DVM, PhD, DACVIM; Alan J. Guthrie, BVSc, PhD

EQUINE

Objective—To evaluate the efficacy of furosemide for prevention of exercise-induced pulmonary hemorrhage (EIPH) in Thoroughbred racehorses under typical racing conditions.

Design—Randomized, placebo-controlled, blinded, crossover field trial.

Animals—167 Thoroughbred racehorses.

Procedures—Horses were allocated to race fields of 9 to 16 horses each and raced twice, 1 week apart, with each of the 2 races consisting of the same race field and distance. Each horse received furosemide (500 mg, IV) before one race and a placebo (saline solution) before the other, with the order of treatments randomly determined. Severity of EIPH was scored on a scale from 0 to 4 after each race by means of tracheobronchoscopy. Data were analyzed by means of various methods of multivariable logistic regression.

Results—Horses were substantially more likely to develop EIPH (severity score ≥ 1; odds ratio, 3.3 to 4.4) or moderate to severe EIPH (severity score ≥ 2; odds ratio, 6.9 to 11.0) following administration of saline solution than following administration of furosemide. In addition, 81 of the 120 (67.5%) horses that had EIPH after administration of saline solution had a reduction in EIPH severity score of at least 1 when treated with furosemide.

Conclusions and Clinical Relevance—Results indicated that prerace administration of furosemide decreased the incidence and severity of EIPH in Thoroughbreds racing under typical conditions in South Africa. (*J Am Vet Med Assoc* 2009;235:76–82)

Horse racing is a popular, multimillion-dollar industry worldwide, but reports of injuries and other physical disorders in racehorses have harmed public perceptions of the sport and challenged the economic viability of the racing industry. In addition, controversy has been generated by use of medications that are perceived to affect the performance or well-being of racehorses. One of the foremost concerns in this regard is the occurrence of EIPH and the use of medications in an attempt to prevent it. Factors that make this an important issue include the frequency of EIPH, the importance of the disease in terms of the performance and well-being of horses, and the common use of prophylactic treatments. At least 80% of racehorses can be expected to develop the condition at some time during their career,[1,2] approximately 60% of sudden deaths during racing have been attributed to pulmonary hemorrhage,[2] severe EIPH has been shown to adversely affect race performance,[3] and EIPH is believed to adversely affect the overall health of racehorses.[4] Beyond this, management and treatment of EIPH have a substantial economic impact, with the cost of treating EIPH estimated to exceed $100 million annually in the United States alone.[4]

Abbreviations

EIPH	Exercise-induced pulmonary hemorrhage
IQR	Interquartile range
NHRA	National Horse Racing Authority of South Africa
OR	Odds ratio
R	South African Rand

Furosemide is the drug most widely used to prevent EIPH in racehorses and is administered on the day of racing to > 92% of Thoroughbred racehorses in North America (approx 400,000 doses/y).[4,5] However, few studies have examined whether furosemide is effective in preventing the development of EIPH, and the studies that have been performed were not conducted

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All authors contributed equally to this study.

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Address correspondence to Dr. Hinchcliff.

under actual racing conditions. Given this lack of evidence and the finding that furosemide can improve the performance of Thoroughbred racehorses,[6] the use of furosemide to prevent EIPH remains controversial. The purpose of the study reported here, therefore, was to evaluate the efficacy of furosemide for the prevention of EIPH in Thoroughbred racehorses racing under typical conditions.

Materials and Methods

Study design—The study was conducted as a randomized, placebo-controlled, crossover field trial. All study participants, including data analysts, were blinded to treatment assignments until statistical analyses related to the primary outcome were completed. The study was conducted at the Vaal Racing and Training facility in Free State Province, Republic of South Africa, between November 20 and 28, 2007, and the study protocol was approved by the institutional animal care and use committees of the University of Pretoria and Colorado State University. For all horses participating in the study, the owner or his or her designee (ie, the trainer) provided informed consent.

Experimental protocol—In an attempt to include horses broadly representative of all horses racing in South Africa, the study was announced at public meetings of trainers, during television programs devoted to horse racing, via racing Web sites, in text messages to trainers, and in advertisements in the local print media inviting owners and trainers to nominate horses for inclusion in the study. Horses considered eligible for participation were Thoroughbred racehorses registered with the NHRA and trained by licensed trainers. Horses were enrolled without knowledge of whether they had previously had EIPH, with the exception that horses with a history of epistaxis during racing or training that had been documented by a veterinarian or steward employed by the NHRA were excluded. At the time horses were nominated for inclusion in the study, the owner or trainer was asked to indicate the specific race or races (eg, 1,300-m race with colts and geldings that had merit ratings ≤ 76) designated for the study during which the horse would be allowed to race.

Horses accepted for inclusion in the study were assigned to race fields on the basis of age, sex, and race record by a professional handicapper who also assigned handicap weights, with each race field consisting of 9 to 16 horses. Enrolled horses raced twice, 7 days apart, with each of the 2 races consisting of the same race field (with the exception of horses withdrawn from the study prior to the second race) and same race distance. Horses carried the same weight, were ridden by the same jockey, started from the same barrier stall, and wore identical tack during the 2 races. Races were run over turf according to the rules of racing of the NHRA, with the exception that administration of furosemide or a placebo prior to each race was permitted for purposes of the present study. In accordance with NHRA rules, blood and urine samples were obtained from selected horses after each race and tested for prohibited medications, including NSAIDs. Owners of horses included in the study were paid a participation fee of R2,000 on completion of the second race. In addition, prize money was paid to the owners of horses that finished first (R28,750), second (R9,200), third (R4,600), fourth (R2,300), or fifth (R1,150) in each race. Prior to each race, trainers were allowed to withdraw (scratch) horses from the race in accordance with the standard rules of racing. Horses that were withdrawn prior to the first race were not allowed to participate in the second race.

Trainers were required to bring participating horses to the racetrack 4.5 hours before the scheduled start time of the race in which they were to compete. As each horse arrived at the track, study personnel confirmed the identity of the horse by checking for a microchip and applied an adhesive tag with a unique identifying number to the mane. Horses were then weighed, placed in stalls, and attended by their grooms. Access to food and water was denied from 4 hours prior to racing until after a tracheobronchoscopic examination was performed following completion of the race. Thirty minutes before the scheduled start of the race, horses were again weighed and moved to the saddling enclosure.

Four hours (± 5 minutes) before the scheduled start of the race, horses were treated with furosemide or a placebo. Each horse received furosemide before one race and a placebo before the other. Treatment order (furosemide prior to the first race and placebo prior to the second race vs placebo prior to the first race and furosemide prior to the second race) was randomly determined by assigning a computer-generated random number to every horse prior to the first race. The first half of each field, as determined by these random numbers, was assigned to receive furosemide prior to the first race and a placebo prior to the second race. The second half of each field was assigned to the opposite treatment order.

Randomization and treatment assignment were performed by an investigator who was not involved in administering any treatments on race days. Individual doses of furosemide[a] (500 mg) and a placebo solution were prepared for all horses prior to the initiation of the study. Each syringe contained 10 mL of solution, and syringes were labeled with horse identification number, race number, and race day. The furosemide solution that was used for the present study had a slight yellow color. Therefore, the placebo solution consisted of saline (0.9% NaCl) solution to which a vitamin B complex solution[b] (0.1 mL/1,000 mL of saline solution) had been added as a coloring agent. Because each 10-mL dose of the placebo solution contained only 0.0001 mL of the vitamin B complex solution, it was considered unlikely to have had any clinically important biological effect, and vitamin B complex solution was not added to the furosemide solution. Furosemide and placebo solutions were administered by IV injection into a jugular vein. Blood samples were collected 15 minutes after treatments were administered and tested for furosemide concentration to verify that the correct treatment had been given.

All races started within 4 minutes of the scheduled start times. At the end of each race, horses were returned to the parade ring, where they were examined by veterinary officials from the NHRA and their tack

was removed. A tracheobronchoscopic examination was then performed. All tracheobronchoscopic examinations were performed by one or the other of 2 teams consisting of 2 veterinarians and 2 lay assistants each. Individuals performing the tracheobronchoscopic examinations were experienced in the procedure, were provided information on the general study protocol, and were specifically asked to thoroughly examine the pharynx, larynx, and trachea to the level of its bifurcation. However, they were blinded to treatment group assignment. All examinations were directly overseen by one of the authors (KWH) and were digitally recorded. After completion of the tracheobronchoscopic examination, horses were released to the care of their trainers.

Maximum environmental temperature on race days ranged from 21.1° to 27.6°C (70.0° to 81.7°F), and minimum environmental temperature ranged from 18.9° to 25.6°C (66.0° to 78.1°F). Maximum humidity ranged from 18% to 73%, and minimum humidity ranged from 14% to 55%. Wind speed during the times that horses raced ranged from 3.4 to 9.2 m/s. A total of 2 mm of rain fell during the time that horses raced on the first race day; 4.2 mm of rain fell on the last of the 4 race days, although this fell after completion of the last race that day.

Assessment of EIPH severity—Digital recordings of each of the tracheobronchoscopic examinations were reviewed by 3 individuals experienced in endoscopic examination of the airway in horses. Individuals scoring the recordings were blinded to identity of the horses and treatment group assignments.

Scoring of EIPH severity was performed by all 3 individuals concurrently, with the digital recording displayed on a large-screen television. Each individual was asked to assign a score from 0 to 4 for severity of EIPH on the basis of a previously reported validated scoring system.[7] Individual scores were then discussed, and if necessary, the examination was reviewed to obtain a consensus score, with consensus scores used in all data analyses.

Data analysis—During design of the study, sample size calculations were performed with standard commercial software.[c] For these calculations, it was assumed that if furosemide were efficacious, the proportion of horses with an EIPH score ≥ 2 would be ≤ 10% following treatment with furosemide, compared with an assumed baseline prevalence of 20% when horses were not treated with furosemide,[3] and that the mean ρ value for repeated observations among subjects would be 0.4. When the α error rate was set at 0.05, sample size calculations indicated that approximately 150 horses would need to complete both arms of the study to achieve a β error rate of 0.2. Assuming that a maximum of 20% of the study subjects would be withdrawn between the first and second arms of the study and that race fields would achieve a minimum of 90% subscription through the use of typical race enrollment methods, we calculated that 12 races with a maximum of 16 horses starting in each race would be required for each arm of the study. No rules for stopping the study or interim analysis of results were put in place.

The primary study outcome was the score for severity of EIPH as determined by means of tracheobronchoscopy. Continuous data were summarized as median and IQR because data were generally not normally distributed, with the exception that differences between pre- and posttreatment body weights of horses were normally distributed and were summarized as mean and SE and elapsed times between the start of racing and tracheobronchoscopy were normally distributed and were summarized as mean and SD. For horses that completed both arms of the study, the EIPH severity score after treatment with furosemide was compared with severity score after treatment with placebo, and the difference between scores was summarized as mean and SD; the Wilcoxon signed rank test was used to determine whether the median difference between scores was significantly different from 0. The Wilcoxon rank sum test was used to compare ordinal and continuous data between groups, and the χ^2 test of homogeneity was used to compare categorical data between groups. The Bowker symmetry test was used to compare paired EIPH severity scores for horses that completed both arms of the study.

Scores for endoscopic severity of EIPH could not be analyzed in their native form (ie, scores of 0 to 4) by means of proportional odds, multinomial logistic regression because assumptions of proportionality were not met. Therefore, scores were dichotomized (0 vs 1 to 4 and 0 or 1 vs 2 to 4) to allow analysis by means of logistic regression. Because various methods have been proposed for analysis of data from crossover studies with binomial outcomes,[8–10] mixed-effects, repeated-measures fixed-effects, and conditional logistic regression models were all used to analyze dichotomized scores. Horse identity was nested within treatment sequence in these analyses to account for random and repeated effects. The primary exposure of interest was treatment (furosemide vs placebo); however, sex, race distance, age, and treatment sequence (furosemide prior to the first race and placebo prior to the second race vs placebo prior to the first race and furosemide prior to the second race) were also evaluated as fixed effects in mixed-effects and repeated-measures modeling. It was not possible to analyze sex, race distance, or age in conditional logistic regression models, as there were no differences in these exposures for paired observations. Age (≤ 3 years old vs ≥ 4 years old) and race distance (1,000, 1,300, or 1,600 m) were analyzed as categorical fixed effects. Exposure variables were analyzed for simple associations with outcome and were included in models with the primary exposure of interest (treatment). Confounding was investigated in multivariable models by evaluating the change in parameter estimates that occurred when variables were included or excluded from the model. Confounding was considered to be present when estimates changed by ≥ 20%. Effect modification was investigated by inclusion of first-order interaction terms. Treatment sequence was included as a random or repeated effect in each model, regardless of whether a significant association could be identified, when treatment sequence was analyzed as a fixed effect. This was considered a conservative method of accounting for incomplete washout,[8–10] even though incomplete washout was not expected.

It was not possible to analyze data on an intent-to-treat basis because tracheobronchoscopy is not routinely

performed after racing and occurrence of EIPH was not known for horses that did not participate. Therefore, data were analyzed on a per-protocol basis. However, use of repeated-measures and mixed-effects logistic regression allowed inclusion of data for horses that only completed the first race (as opposed to requiring that horses complete both arms of the study to be included in analyses), which provided some assurance that missing data for horses that were withdrawn (scratched) did not strongly bias the conclusions of the study.

Analyses were performed with commercial software.[d] A priori, values of $P \leq 0.05$ were determined to be significant.

Results

A total of 328 horses were nominated for inclusion in the study. Of these, 193 (77 females and 116 stallions and geldings) were enrolled in the study by the professional handicapper. Of the 193 horses enrolled in the study, 155 competed in both races, 12 competed only in the first race, and 26 did not compete in either race (**Table 1**). Horses that participated in the study were from 40 stables (median, 3.5 horses/stable; range, 1 to 14 horses/stable). Twenty-three trainers withdrew at least 1 horse from a study race. Demographic characteristics of horses that did not compete in either race did not differ significantly from characteristics of horses that competed in at least 1 race (**Table 2**).

Two horses that competed in both races would not allow tracheobronchoscopy to be performed after either race because of their fractious nature, and 1 horse would not allow tracheobronchoscopy to be performed after the second race. Mean ± SD time between the start of racing and tracheobronchoscopy was 41.6 ± 5.9

Table 1—Details of racing conditions for Thoroughbred racehorses enrolled in a study of the efficacy of furosemide for prevention of EIPH.

Race day	Race No.	Distance (m)	Class	Horses nominated	Horses enrolled*	Raced in first race	Raced in second race
A	1	1,300	Maiden fillies	38	18	15	12
A	2	1,300	Maiden colts and geldings	32	17	14	14
A	3	1,300	Maiden colts and geldings	31	18	15	14
A	4	1,600	Maiden colts and geldings	27	14	14	13
A	5	1,600	Maiden colts and geldings	26	14	13	11
A	6	1,600	Maiden fillies	43	18	15	13
B	1	1,000	Fillies and mares (merit ratings ≤ 68)	22	13	9	9
B	2	1,000	Colts and geldings (merit ratings ≤ 72)	37	18	16	16
B	3	1,300	Colts and geldings (merit ratings ≤ 76)	56	18	15	13
B	4	1,300	Fillies and mares (merit ratings ≤ 72)	39	16	15	14
B	5	1,600	Fillies and mares (merit ratings ≤ 68)	35	12	12	12
B	6	1,600	Colts and geldings (merit ratings ≤ 68)	38	17	14	14
			Total	**328**	**193**	**167**	**155**

Of the 328 horses nominated for inclusion in the study, 235 were nominated for 1 race, 90 were nominated for 2 races, and 3 were nominated for 3 races. Horses enrolled in the study raced twice, 7 days apart, with each of the 2 races consisting of the same race field (with the exception of horses withdrawn from the study prior to the second race) and same race distance. Each horse received furosemide (500 mg, IV) before one race and a placebo (saline solution) before the other, and severity of EIPH was scored immediately after the race by means of tracheobronchoscopy.
*Included starters and reserves; the maximum number of horses in each race was 16 starters and 2 reserves.

Table 2—Demographic characteristics of Thoroughbred racehorses enrolled in a study of the efficacy of furosemide for prevention of EIPH.

Variable	Nominated but not enrolled	Raced at least once	Enrolled but did not race	*P* value
No. of horses	135	167	26	NA, NA
Age	4 (3–5)	4 (3–4)	4 (4–5)	0.39, 0.12*
Sex				0.86, 0.34†
Stallion	9	13	0	
Gelding	69	88	15	
Female	57	66	11	
Assigned weight (kg)	NA	57 (56–58)	58 (55–58)	NA, 0.45*
Merit rating‡	65 (55–72)	65 (59–69)	58 (54–65)	0.28, 0.02*
Lifetime No.				
Starts	12 (5–21)	10 (3–22)	12 (8–21)	0.35, 0.19*
First-place finishes	1 (0–2)	0 (0–1)	1 (0–1)	0.06, 0.79*
Second- and third-place finishes	2 (0–5)	2 (0–4)	2 (1–5)	0.50, 0.15*
Finishes earning money	4 (2–9)	4 (0–9)	4.5 (3–8)	0.56, 0.35*
Lifetime earnings ($)	536,250 (220,000–1,018,700)	60,850 (23,000–111,745)	48,750 (23,550–94,490)	0.21, 0.42*

Data are given as median (IQR) or number of horses. *P* values are given as the *P* value for comparisons between horses that were nominated but not enrolled and horses that were enrolled, followed by the *P* value for comparisons between horses that raced at least once and horses that were enrolled but did not race.
**P* value from Wilcoxon rank sum test. †*P* value from χ^2 test of homogeneity. ‡Excludes maidens.
NA = Not applicable.

minutes when horses were treated with furosemide and 42.1 ± 6.0 minutes when horses were treated with saline solution. These values were not significantly (P = 0.63) different.

Scores for endoscopic severity of EIPH ranged from 1 to 4 in 89 of 161 (55.3%) horses after administration of furosemide and in 125 of 156 (80.1%) horses after administration of saline solution (**Figure 1**); these proportions were significantly (P < 0.001) different. For the 152 horses examined after both races, 87 (57.2%) had EIPH (ie, severity score ≥ 1) after administration of furosemide, whereas 120 (78.9%) had EIPH after administration of saline solution (**Table 3**). None of the horses had severe EIPH (ie, a score of 3 or 4) after administration of furosemide. Overall, 81 of the 120 (67.5%) horses that had EIPH after administration of saline solution had a reduction in EIPH severity score of at least 1 when treated with furosemide. Mean ± SD reduction in EIPH severity score after furosemide administration in the 120 horses that had EIPH after administration of placebo was 0.63 ± 0.08; median reduction in EIPH severity score was significantly (P < 0.001) different from 0.

Results of mixed-effects, repeated-measures fixed-effects, and conditional logistic regression analyses all indicated that horses had significantly lower odds of developing EIPH (ie, severity score ≥ 1) or moderate to severe EIPH (ie, severity score ≥ 2) following administration of furosemide, compared with odds following administration of saline solution (**Table 4**). Horses were 3.3 to 4.4 times as likely to have an EIPH score ≥ 1 following administration of saline solution than they were following administration of furosemide and were 6.9 to 11.0 times as likely to have an EIPH score ≥ 2 following administration of saline solution than they were following administration of furosemide.

Although results of mixed-effects and repeated-measures fixed-effects logistic regression suggested that horses that were ≥ 4 years old were more likely to develop EIPH (ORs, 1.8 and 1.9, respectively; P = 0.04 and 0.07, respectively), no effect modification (ie, an interaction between age and treatment) was detected, and age did not appear to be a confounding variable in these analyses. Development of EIPH was also not associated with sex (P = 0.30 and 0.38, respectively), distance raced (P = 0.38 and 0.99, respectively), or treatment sequence (P = 0.69 and 0.99, respectively) in these analyses.

Mean ± SE weight loss during the 4 hours prior to the start of the race was 12.7 ± 0.33 kg (27.9 ± 0.73 lb) when horses were given furosemide (n = 160) and 5.4 ± 0.28 kg (11.9 ± 0.62 lb) when horses were given saline solution (155). These values were significantly (P < 0.001) different. There was no association between weight loss and development of EIPH, even when controlling for treatment (P ≥ 0.50).

Analysis of blood samples collected 15 minutes after administration of furosemide or placebo confirmed the presence of furosemide in all horses after administration of furosemide and in none of the horses after administration of the placebo.

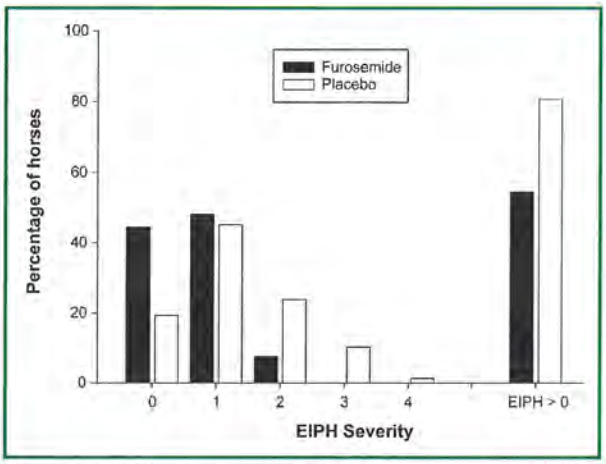

Figure 1—Distribution of scores for endoscopic severity of EIPH in Thoroughbred horses that raced following administration of furosemide (500 mg, IV; n = 161) or a placebo (saline solution; 156).

Table 3—Cross-classification of scores for endoscopic severity of EIPH following racing in 152 Thoroughbred racehorses competing twice under similar conditions each time, except that furosemide (500 mg, IV) was administered prior to one race and a placebo (saline solution) was administered prior to the other.

EIPH score when administered furosemide	EIPH score when administered placebo					
	0	1	2	3	4	Total
0	21	32	10	2	0	**65**
1	10	32	21	11	1	**75**
2	1	3	4	3	1	**12**
3	0	0	0	0	0	**0**
4	0	0	0	0	0	**0**
Total	**32**	**67**	**35**	**16**	**2**	**152**

Potential EIPH scores ranged from 0 to 4. Distribution of scores differed significantly (Bowker symmetry test; P < 0.001) between treatments.

Table 4—Results of logistic regression analysis of EIPH severity scores for Thoroughbred racehorses enrolled in a study of the efficacy of furosemide for prevention of EIPH.

Logistic regression analysis method	OR	95% CI	*P* value
Development of EIPH (ie, severity score ≥ 1)			
Mixed-effects	3.4*	2.0–5.7	< 0.001
Repeated-measures fixed-effects	3.3*	2.1–5.2	< 0.001
Conditional	4.4†	2.2–8.8	< 0.001
Development of moderate to severe EIPH (ie, severity score ≥ 2)			
Mixed-effects	7.1*	3.6–14.1	< 0.001
Repeated-measures fixed-effects	6.9*	3.7–13.0	< 0.001
Conditional	11.0†	4.0–30.3	< 0.001

*Odds ratio was adjusted for age. †Odds ratio was not adjusted for age, because this variable did not differ between paired observations.
CI = Confidence interval.
Odds ratios represent the odds that horses would develop EIPH following administration of a placebo (saline solution), compared with the odds that they would develop EIPH following prerace administration of furosemide (500 mg, IV).

Discussion

Results of the present study indicated that prerace administration of furosemide decreased the incidence and severity of EIPH in Thoroughbreds racing under

typical conditions in South Africa. Specifically, horses were substantially more likely to develop EIPH (severity score ≥ 1; OR, 3.3 to 4.4) or moderate to severe EIPH (severity score ≥ 2; OR, 6.9 to 11.0) following administration of saline solution than following administration of furosemide, and the estimated proportion (unadjusted for repeated measures or confounding) of horses that developed EIPH (ie, severity score ≥ 1) following administration of furosemide (89/161 [55.3%]) was significantly lower than the estimated proportion that did following administration of saline solution (125/156 [80.1%]). In addition, 81 of the 120 (67.5%) horses that had EIPH after administration of saline solution had a reduction in EIPH severity score of at least 1 when treated with furosemide.

Important strengths of the present study include the large number of horses examined, the evaluation of horses after standard race conditions, and the use of horses from a population expected to be at risk for developing EIPH (ie, Thoroughbred racehorses in active training and racing). Because various methods have been recommended for analysis of data from crossover studies, we elected to use mixed-effects, repeated-measures fixed-effects, and conditional logistic regression to analyze our data, and results of all 3 analyses were consistent. The strong association between furosemide administration and protection against development of EIPH made it unlikely that unidentified confounding factors or other biases were solely responsible for this effect. The use of a crossover study design enhanced the statistical power of the study over that associated with a parallel-group study design.[11]

Examination of drug effects under actual conditions of use has long been recognized as the best measure of efficacy in human medicine, with randomized, controlled, clinical trials considered to provide the highest degree of evidence for efficacy.[12] However, such trials can be difficult to perform in veterinary medicine, and we are not aware of any previous such studies that have addressed the effects of various preventive measures on the development of EIPH in racehorses.

Results of the present study provide strong evidence that furosemide can help prevent the development of EIPH in Thoroughbred racehorses. As such, its use in racehorses might be justifiable, assuming that other regulatory and policy issues important to the integrity of the sport are adequately addressed.

The mechanism by which furosemide prevents EIPH is unclear, and the present study was not designed to address this issue. It has been speculated that furosemide-induced reductions in body weight are indicative of reductions in body water and intravascular fluid volume and that these reductions in body water and intravascular fluid volume attenuate the exercise-induced increase in pulmonary arterial blood pressure typically associated with exercise, with a consequent reduction in the incidence of alveolar capillary rupture and decreased hemorrhage.[13–15] The amount of weight lost by horses in the present study after furosemide administration was consistent with the amount of weight loss in horses administered furosemide under experimental conditions.[16–18] However, weight loss does not appear to be directly related to the mechanism by which furosemide prevents EIPH, in that we did not identify an association between amount of weight lost and prevention of EIPH in the present study. We have previously shown that EIPH adversely affects the performance of racehorses and that treatment with furosemide improves race performance,[3,6] and results of the present study would seem to suggest that the improved performance associated with furosemide could potentially be attributed to prevention or mitigation of EIPH.

For the present study, we believed that evaluating a large number of horses under actual racing conditions was important because previous studies[13,19] have used experimental models (eg, horses running on a treadmill) that might not reflect racing conditions, had low statistical power because of low numbers of horses, or had limitations in study design or statistical analysis that may have affected their results. Two previous studies[1,20] have examined the effect of furosemide in racehorses under field conditions, although with differing conclusions regarding efficacy. However, neither study was conducted as a randomized, controlled trial, and the data analysis in one of these studies[21] has been criticized.

An important concern with crossover studies is that the time between arms of the study (ie, the washout period) must be sufficiently long to preclude any residual effects associated with the previous treatment. In the present study, we elected to use a washout period of 7 days on the basis of the reported short elimination half-life of furosemide in horses (β half-life, 24 minutes; γ half-life, 177 minutes) and the brief (1-hour) diuretic effect of the drug.[22] The fact that we did not detect furosemide in any of the blood samples collected 15 minutes after administration of saline solution suggested that the washout period was adequate. In addition, there was no evidence that treatment order had an effect on the results of our statistical analyses. Finally, even if there had been a carryover effect in horses that had been treated with furosemide first, this would have acted to make it more difficult to identify a difference between the 2 treatments.

Furosemide reduces mucociliary clearance in humans and causes bronchodilation in ponies with recurrent airway obstruction.[23,24] It is possible, therefore, that furosemide did not actually decrease alveolar bleeding in the present study but simply decreased the rostral progression of blood from the alveoli, diminishing the amount of blood in the trachea at the time of endoscopic examination and resulting in an artifactually low EIPH severity score. Alternatively, bronchodilation secondary to furosemide administration might have favored rostral movement of blood and made the endoscopic score appear worse than it would have been had furosemide not been administered. We believe that the magnitude of either of these potentially conflicting effects is likely to be small in horses without recurrent airway obstruction and bronchoconstriction and would have been unlikely to have materially affected the overall conclusions of the present study.

The present study was performed in South Africa for logistic reasons. However, South Africa has a well-regulated racing industry with horses comparable to those racing in other parts of the world. We believe, therefore, that our results can be generalized to other

racing jurisdictions, particularly given the relative genetic homogeneity of Thoroughbred racehorses,[25] the similarity in training techniques and racing conditions throughout the world,[26] and the characteristics of horses included in our study. Although racing and training conditions in other parts of the world do differ from those in South Africa in minor respects, we do not have any evidence that any of these differences have been demonstrated to have an impact on the frequency or severity of EIPH. Therefore, we believe that results of the present study are relevant to horses racing worldwide.

a. Salix, Intervet SA (Pty) Ltd, Isando, South Africa.
b. Kryovite B Co Super, Kyron Laboratories (Pty) Ltd, Benrose, South Africa.
c. PASS 2007, Number Cruncher Statistical Systems, Kayesville, Utah.
d. SAS, version 9.2, SAS Institute Inc, Cary, NC.

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Testing Integrity

November 9, 2011

Mr. Richard A. Violette, Jr.
New York Thoroughbred Horsemen's Association, Inc.
P.O. Box 170070
Jamaica, NY 11417
Telephone 518.581.1034
Fax 518.581.1037
Email: info@nytha.com
Ph 516 236 2313

Re: "Use of lasix under today' protocols does not compromise the integrity of the testing".

Dear Mr. Violette,

Thank you for your time on the telephone today and your inquiry as to whether or not the use of Lasix under today's protocols does not compromise the integrity of the testing process, as set forth in your attached e-mail [attachment number one]

My analysis and opinions in this matter are based on my knowledge of the relevant scientific literature and of equine pharmacology and the detection and pharmacokinetics and pharmacodynamics and chemistry of drugs in horses. My background includes my training and experience as a licensed veterinarian, [MVB, University College Dublin, 1964], a Member of the Royal College of Veterinary Surgeons [MRCVS, London, England], 1964 to date, and licensed in Kentucky, Kentucky Veterinary License, NS-1053], a doctoral level pharmacologist [PhD University of Toronto, 1970] and a board-certified toxicologist, Diplomate, American Board of Toxicology [DABT],1980 to date, as set forth in my attached curriculum vitae [Appendix #1] or as can be found at www.ThomasTobin.com.

With respect to the above question let me simply say that when the Lasix protocols in place today were introduced approaching 30 years ago, they were at that time and still are fully protective of the integrity of the testing process. Since then, analytical testing has increased approximately 1 million fold in sensitivity, and especially the sensitively of blood plasma/serum testing. This is important because, to our knowledge, Lasix does not in any way significantly interfere with plasma concentrations of drugs, and as such does not in any way interfere with the testing process in blood.

With regard to testing in urine, under the Lasix protocols in place today, there is no significant interference whatsoever with urine testing for drugs, as set forth in the recent review paper in this area authored by my colleague Dr. Richard Sams, closing paragraph, "REGULATORY ISSUES". [attachment number 2]

So, the answer to your question is unequivocally yes, the use of Lasix under today's Lasix protocols does not compromise the integrity of the testing process in any way whatsoever.

If anything about this opinion is unclear or could be better expressed or if I can be of any further assistance to you please do not hesitate to contact me; the meantime, I remain,

Yours sincerely,

Thomas Tobin
MVB, M.Sc., Ph.D., MRCVS,
Diplomate, American Board of Toxicology [DABT]
Associate Member, Association of Official Racing Chemists
Founding Member, American College of Veterinary Pharmacology
Veterinarian, Pharmacologist and Toxicologist
Nine Mile Farm
5301 Bethel Rd
Lexington
KY 40511

Copy: file
Mr. Richard Violette, 360 Bauer Place, Mineola N. Y. 11501

Attachments 1-2
Appendix 1 www.thomastobin.com or Attached vitae

New York Drug Testing and Research Program
777 Warren Road Ithaca, NY 14850
Telephone: 607-882-9065 Fax: 607-882-9067

November 8, 2011

Mr. Richard Violette
President
New York Thoroughbred Horsemen's Association
PO Box 90
Jamaica, NY

Dear Mr. Violette:

I am responding to your recent inquiry concerning furosemide and its potential to mask the presence of other drugs in equine drug testing and make them more difficult to detect.

Furosemide does not interfere with drug detection provided that it is administered at least 4 hours prior to racing and within an intravenous dose range of 250 to 500 mgs. Furosemide is regulated in New York, as it is in most racing jurisdictions, through a plasma threshold and urine specific gravity. In New York, furosemide can only be administered by a regulatory veterinarian, not a private veterinarian.

In addition to these regulatory precautions in place at the track, the analytical instruments used in drug testing in New York are much more sensitive than those used even several years ago. New, ultra-sensitive instrumental testing combined with the regulatory control outlined above precludes the possibility of furosemide interference with drug testing.

Sincerely,

George Maylin DVM, PhD
Director

Medications
Olympics-Horse Racing

UNITED STATES ANTI-DOPING ASSOCIATION
EXAMPLES OF PERMITTED MEDICATIONS UP TO AN EVENT

(WITHDRAWAL TIMEFRAME FOR USAGE IN HORSERACING IN NEW YORK)

Examples of **PERMITTED** Medications

Effective January 1, 2009

ADD/ADHD: Strattera (1 week out)

Anesthetics: All local and local injections with epinephrine permitted (96 hours out)

Antacids: Di-Gel, Gaviscon, Maalox, Mylanta, Tums (24 hours out)

Anti-Anxiety: Atarax, Ativan, Buspar, Librium, Valium, Vistaril (1 week out)

Antibiotics: All are permitted (24 hours out)

Anti-Depressants: Celexa, Cymbalta, Effexor, Paxil, Prozac, Wellbutrin, Zoloft (1 week out)

Anti-Diabetics: Actos, Amaryl, Avandia, Glucophage, glipizide, Glucotrol, glyburide, metformin (1 week out)

Anti-Diarrheals: Diphenoxylate w/atropine, Imodium, kaolin w/pectin, Kaopectate, Lomotil, Lonox, loperamide, Pepto Bismol (24 hours out)

Topical Antifungals: Clotrimazaole, Cruex, Desenex, Lamisil, Lotrimin, Micatin, Monistat, Mycostatin,Tinactin (96 hours out)

Anti-Nausea/Anti-vertigo: Antivert, Bonine, Bucladin S, Compazine, diphenhydramine, Dramamine, Emetrol, Motion Aid, Tigan (1 week out)

Antiviral: Acyclovir, didanosine, Famvir, Relenza, stavudine, Tamiflu, Valtrex (96 hours out)

Asthma: Accolate, cromolyn sodium, Intal, ipratropium, nedocromil sodium, Singulair, Spiriva, theophylline, Tilade (96 hours out)

Cold/Allergy Medications:
Antihistamines/Decongestants: Allegra, Allegra-D, Benadryl, Benadryl-D, cetirizine, chlorpheniramine, clamastine, Clarinex, Claritin, Claritin-D, diphenhydramine, fexofenadine,

loratadine, naphazoline, oxymetazoline, phenylephrine, pseudoephedrine, tetrahydrozoline, xylometazoline, Zyrtec, Zyrtec-D (96 hours out)
CAUTION: Vicks Vapor Inhaler is prohibited

Combination Cold Medications: Actifed cold & sinus, Advil cold & sinus, Alka-Seltzer Plus (cold & cough, cold & sinus, cold & flu), Chlor-Trimeton (-D, allergy), Comtrex, Coricidin (-D, HBP, cold, flu & sinus, cough & cold), Drixoral (cold & allergy, allergy sinus), Mucinex (-D, DM), Robitussin (severe congestion, cold & cough, CF, PE, DM), Sudafed (-PE, sinus, cold & allergy, maximum strength sinus), TheraFlu (flu, cold & cough, severe cold and congestion, flu & cold), Triaminic (cold & cough, allergy congestion, cold, allergy & sinus), Tylenol (allergy sinus, flu, cold, sinus, multi-symptom), Vicks (44D, Dayquil, Nyquil)
Cough preparations: Codeine, dextromethorphan, hydrocodone (1 week out)
Expectorant: Guaifenesin (96 hours out)
CAUTION: Combination cold medications may contain prohibited substances

Contraceptives: Alesse, Apri, Aviane, Desogen, Estrostep, Kariva, Loestrin, Lo-Ovral, Mircette, Microgestin, Necon, NuvaRing, Ortho-Cyclen, Ortho Evra patch, Ortho-Tri-Cyclen, Ovcon, Seasonale, Sprintec, Tri-nessa, Triphasil, Trivora, Yasmin, Yaz, Zovia (96 hours out)

Ear Preparations: Auralgan, Auro Ear Drops, Cerumenex, Ciprodex Otic, Cipro HC Otic, Cortisporin Otic, Debrox, Murine Ear Drops, Otic Domeboro (96 hours out)

Eye Preparations: Alrex, Artificial Tears, Blephamide, Cortisporin Ophthalmic, Maxitrol, Murine Plus, Mycitracin, Naphcon-A, Neo-Synephrine, Ocu-Pred, Patanol, Pred-Forte, oxymetazoline, Relief, tetrahydrozoline, Vasocon-A, Visine (96 hours out)

Hemorrhoidals: Anusol, Preparation H. Corticosteroids in creams or ointments used externally are allowed (Systemic use of a corticosteroid is prohibited in-competition and requires an approved TUE) (48 hours out)

Laxatives/Stool Softeners: Colace, Correctol, Dulcolax, Ex-Lax, Fibercon, Fleet Enema, Metamucil, Miralax, sennosides, Senokot (N/A)

Topical Preparations: Aspercreme, Ben-Gay, capsaicin, Flex-All 454, Icy Hot Balm, Myoflex Cream, Sportscreme, Vicks Vaporub, Zostrix, Zovirax, topical skin corticosteroids (24 to 96 hours out)

Muscle Relaxants: Baclofen, Cyclobenzaprine, Flexeril, Norflex, Skelaxin, Soma, Zanaflex (96 hours to 1 week out)

Pain/Anti-Inflammatory: Acetaminophen, Advil, Aleve, aspirin, Bufferin, Celebrex, codeine, Dolobid, Ecotrin, hydrocodone, ibuprofen, Lyrica, meloxicam, Mobic, naproxen, Neurontin, piroxicam, propoxyphene, tramadol, Tylenol (plain, ex-strength), Ultram
Non-steroidal anti-inflammatory agents (NSAIDS): All are permitted (except famprofazone) (96 hours out-if non-narcotic - to one week – if narcotic)

Sedatives/Sleep Aids: Ambien(-CR), Antivert, Ativan, Compoz, Dalmane, diphenhydramine, Halcion, Lunesta, Nytol, Restoril, Rozerem, Sominex, Sonata, trazodone, Unisom, Valium, Xanax (1 week out)

Stomach/Ulcer Medications: Aciphex, Axid, Carafate, Nexium, Pepcid, Prevacid, Prilosec, Protonix Tagamet, Zantac (24 hours out)

Vaginal Preparations: AVC, Femstat, Gyne Lotrimin, Metrogel, Monistat, Mycelex, Mycostatin, Terazol, Vagistat (N/A)

NOTE: Glucocorticosteroids: **All topical administrations for skin, otic (ear), ophthalmic (eye), nasal (nose), buccal (inside mouth), and iontophoresis or phonophoresis are permitted and do not require any filing. Inhalation and local, epidural and intra-articular injections require a Declaration on the DCOR at collection for in-competition use. Systemic use is prohibited in-competition and requires a complete approved TUE.** (48 hours out)

Check the USADA Guide for a more extensive list of permitted substances.
TUE: Therapeutic Use Exemption
IF: International Federation

USADA DIETARY SUPPLEMENT WARNING
Many dietary supplements (vitamins, minerals, amino acids, homeopathics, herbs, energy drinks), which are sold over the counter or through the Internet, contain substances that are prohibited by the World Anti-Doping Code. Since anti-doping rules make the presence of a prohibited substance in an athlete's urine a doping offense regardless of how the substance got there, any athlete who takes a dietary supplement does so at his or her own risk of an adverse analytical finding and a doping violation.

IT IS THE ATHLETE'S RESPONSIBILITY TO CHECK THE STATUS OF ALL MEDICATIONS AND TO KNOW THE RULES OF HIS/HER SPORT

Handlers Hope Lasix Will Help Private Terms Regain Lost Form

[FINAL Edition]
The Washington Post (pre-1997 Fulltext) - Washington, D.C.
Author: Vinnie Perrone
Date: Jun 26, 1988
Start Page: d.15
Section: SPORTS
Text Word Count: 1449

For 23 years, Edward (Stimey) Banks has toiled in the relative obscurity of the race track backstretch. As a groom, he's devoted his adult life to the care of racehorses-feeding them, bathing them, brushing them, bandaging them-with dreams that one day he would get to manage a truly exceptional thoroughbred.

In February, after spending the last four years under trainer Ron Alfano, Banks went to work for Charlie Hadry, who assigned him four horses. When another of Hadry's grooms quit, Banks was given that groom's four horses instead.

One of them, an aggressive dark bay 3-year-old colt with a penchant for biting, ran in the General George Stakes at Laurel three days later. But even as he watched the colt win after encountering trouble through the far turn, Banks had no idea that Private Terms could be the horse he'd been after for nearly a quarter-century.

That realization would come in Aqueduct's Gotham Stakes almost two months later, when Private Terms conceded 12 pounds to favored Seeking The Gold and beat him by nearly a length.

"After watching him in the General George, I knew he had ability to be a real nice horse," Banks said. "But when I saw what he did to Seeking The Gold, I couldn't believe it. I'd had some stakes horses when I worked for Dick Delp-horses like Dairy Bar and Count My Love-but they don't even compare."

When Private Terms followed with a victory in the Wood Memorial, he moved his unbeaten streak to seven races and became the early Kentucky Derby favorite.

"What I couldn't believe," Banks said, "was the way he acted after the race. He was strutting all the way to the detention barn and he bounced all the way back. He'd just beaten the best 3-year-olds in the country, and he was ready to do it again."

It is for a love of animals, Banks said, that he has endured the great ambiguity of his profession. Horses' victories generally are credited to a jockey's ride or a trainer's methods of preparation, but the groom spends the most time with the horse and best knows its mannerisms.

At Churchill Downs several days before the Kentucky Derby, as he attempted to absorb the magnitude of his charge's achievement, Banks first suspected something was wrong with Private Terms.

"He shines naturally, but in Kentucky his coat had a dull look to it," Banks said. "I knew something was wrong inside.

Banks noticed the colt digging through his stall bedding. He seemed to be trying to get to the dirt beneath it, "like he wanted to cool his belly.

"Thoroughbreds are domesticated animals. The same problems that exist in wild horses are taken care of by nature. If a wild horse has bucked shins, he'll go down to a river and stand in mud; with a thoroughbred, man has to diagnose the problems for him. The way Private was at Churchill Downs, maybe that was his way of telling me something was wrong."

After Banks brought Private Terms to the paddock for the Derby, he walked toward the track and looked up at the grandstand. "I thought, `Damn, we're really here,' " he said. "I don't get rattled too easy, but I was shook."

A few minutes later, 3-to-1 favorite Private Terms struggled to finish ninth. In the test barn following the race, both Hadry and Banks heard the colt cough several times.

"I thought maybe he got some dirt caught in his throat," Hadry said.

Private Terms had two workouts between the Derby and Preakness. After each one, Banks waited for the colt to cough; he never did.

Nonetheless, Private Terms failed to run his race in the Preakness. He wound up fourth out of nine, but his signature stretch move again was absent.

When Private Terms began hacking after the race, Hadry called for a veterinarian. An endoscopic examination by Dr. Ralph Yergey disclosed a significant amount of blood in Private Terms' respiratory system.

"He probably bled in the Derby," Hadry said, "because he ran the same way in the Preakness, and we know he bled then."

Kentucky's rules regarding use of the anti-bleeding medication furosemide, or Lasix, are less restrictive than Maryland's. "If I ever went down there again," Hadry said, "I'd probably give a horse 3 or 4 cc's of Lasix if I could just to be sure. But I didn't use anything on Private because I didn't figure at the time that I needed it. I hadn't used anything before, and everything seemed to be goin' so well, I figured why mess with it?"

Now Lasix will become a staple of Private Terms' racing career. He's received an injection of the diuretic before each of his three workouts since the Preakness, and he'll get it again before running in Sunday's $100,000-added Governor's Cup Handicap at Pimlico, in which he will be the 126-pound highweight and a big favorite.

With Private Terms entered in the 1 1/8-mile race, only four other trainers saw fit to test him. The four challengers are 2-year-old Maryland-bred champion Trap Line (115 pounds); the Jack Van Berg-trained Din's Dancer (112), whom Private Terms defeated by three lengths in the Derby; Woodlawn Stakes winner Freezees (110) and Second Lieutenant (107). Leading jockey Kent Desormeaux has the mount on Private Terms.

By his handlers' best estimates, Private Terms has gained 200 to 250 pounds since the Preakness

and has become a ton more impertinent.

"The Lasix hasn't dulled him like it does to a lot of horses," Banks said. "He's always been kind of hyper in the stall; now, after he goes out {onto the track} in the morning, from the time I pick him up at the eighth {-mile} pole to the time we get back {to the barn}, he's bitin' at me and snappin' at me. When he's cooling out, I have to put the shank in his mouth because he's practically off the ground. The easiest way to get along with him now is to bribe him. He loves butterscotch candies and carrots."

As Banks brushed Private Terms one morning last week, the colt pranced around skittishly, then slammed his right foot against the wall of his wooden stall. Banks released him from the shank, whereupon Private Terms tried to bite the groom's right shoulder. When Banks attempted to apply ointment to a tiny sore on Private Terms' forehead, the colt tossed his head.

"He's been a lot worse than this since he started getting Lasix," Banks said. "He got to being such a bear, especially coming off the track, that I had to have Junior {assistant trainer Charlie Hadry Jr.} take over a couple of times."

The elder Hadry reiterated his belief that the use of Lasix in no way diminishes Private Terms' status as a racehorse of high quality. It's not a stimulant, Hadry said, but a drug that rids the body of surplus fluids and simply will allow Private Terms to run to his potential.

Owner/breeder Stuart Janney also has come to espouse the merits of Lasix, though it has taken him many years to do so.

"I know I was very much opposed to using Lasix or anything else at one time," said Janney, 80, who bred the great filly Ruffian and retained her bloodlines in producing Private Terms. "But I've had it happen so many times to so many of my horses that I don't feel that way anymore. I've gotten to be an old man, and I even have to take Lasix once in a while."

If all goes well in the Governor's Cup, Janney plans to send Private Terms to Monmouth Park in Oceanport, N.J., for the $500,000-added Haskell Invitational on July 30. Beyond that, he said, nothing has been decided; however, Janney did say he would like to try the colt on turf, and he did not dismiss the possibility of the Breeders' Cup in November.

When young Hadry said last week that he couldn't wait for Private Terms to test his mettle on grass, his father balked. "I'd be damn particular puttin' him on grass," the trainer said, " 'cause at the end of the year those courses get to be rough. They're all wore out. After all that's gone on, the last thing he needs to do is take a bad step.

"He may have something to prove to some people, but not to me. I still think he's the best 3-year-old in the country . . . I'll tell you one thing: He won't run a bad race Sunday, not unless somethin' drastic happens between now and then."

[

Lasix study should end calls to ban use – professor

July 3, 2009

A study showing that the drug furosemide, commonly called Lasix, reduces lung bleeding in thoroughbred racehorses should put an end to calls to ban the drug, a university professor believes.

"This should pretty much stop the efforts to restrict the use of furosemide dead in its tracks," said Michael Davis, a physiological sciences professor and Oxley Endowed Chair in Equine Sports Medicine at Oklahoma State University's Centre for Veterinary Health Sciences.

"People who are advocating the elimination of furosemide have to explain why they want to deny a horse medicine that has been shown to be beneficial to the horse's health and well being."

Furosemide is widely used in the horse racing industry in North America but is banned on racedays in all other countries. More than 90 per cent of racing thoroughbreds and 50 per cent of racing standardbreds in the United States and Canada are given furosemide a few hours before racing to treat bleeding.

Davis believes the results of the study could change the future of the horse racing industry.

The study, led by Dr Kenneth Hinchcliff, demonstrated conclusively that furosemide, also marketed as Salix and Furoject, reduced the occurrence and severity of exercise-induced pulmonary hemorrhage (EIPH) in horses under actual racing conditions.

"We have been giving furosemide to horses for a long time without any solid scientific proof that it did anything beneficial for the horse," explains Davis.

"The racing industry went along with it. There was no proof that it did or that it didn't benefit the horse. However, the use of medications in racehorses has been getting a lot of negative press recently.

"Some people believe horses just need hay, oats and water, while others perceive that the race horses are drugged up monsters."

Davis points to the racing industry's efforts to get stronger on the rules to keep public interest.

A major problem with the use of furosemide, he said, was a couple of studies a few years ago showing that furosemide, administered the way it is typically done in racing conditions, could make the horse run faster.

"The racing industry found itself in the position of not having proof it was any benefit but it was, in fact, a performance enhancer, which was becoming difficult to defend.

"This study provides the proponents of furosemide with the proof they needed that it does provide a benefit to the horse," he adds.

Davis said he believed the racing industry in North American currently supported the use of furosemide. There are rules attached to it in terms of how much can be given to a horse, how soon before the race it can be administered, and which horses can receive it.

Davis believes the study is a step in the right direction for the horse industry.

"It was an incredibly expensive and difficult study to do and was supported by the racing industry," he explains.

"Extremely well designed, and conducted by investigators with impeccable integrity, the study was designed to honestly investigate furosemide, not to come up one way or another.

"Had it shown no benefit to using furosemide, then the racing jurisdictions would have started outlawing the drug. If it had shown no benefit, that would have been equally defensible. Bottom line, the conduct of the study demonstrates in deed and not just talk that the racing industry is, in fact, trying to improve the conditions of the sport."

http://www.horsetalk.co.nz/news2009/07/024.shtml

Nicky Henderson tells vets' inquiry 'plenty' used banned drug

• Trainer says he was unaware substance was illegal
• Horse was injected before Huntingdon race in 2009

Greg Wood

Tuesday 15 February 2011 14.42 EST

Nicky Henderson gave evidence today at a hearing into the conduct of a vet in his yard. Photograph: Alan Crowhurst/Getty Images

Nicky Henderson, who was banned from making entries for three months in 2009 after one of his horses tested positive for tranexamic acid, has told a hearing at the Royal College of Veterinary Surgeons that "plenty of trainers" were using the banned blood-clotting agent at the time.

Henderson, one of the most senior and successful trainers in the Lambourn area, was giving evidence at a disciplinary hearing of James Main, the vet who injected Moonlit Path, a six-year-old mare owned by the Queen, with tranexamic acid a few hours before she was due to contest a race at Huntingdon in February 2009. Main has admitted injecting Moonlit Path, but denies that he knew, or ought to have known, that this was against the Rules of Racing.

Henderson told the hearing that at the time of the Huntingdon race he was unaware that tranexamic acid, which can aid the recovery of horses who have suffered from bleeding in the lungs, was a banned substance. Asked by Kieran Coonan QC, representing Main, whether he knew of other trainers using the same substance, Henderson said: "I do now." He added: "I didn't before that, but I do now because of the amount of trainers who came up to me after the case and said 'I'm not using it any more'." Coonan continued: "The inference being?" Henderson replied: "That there were plenty of trainers who were using it."

Henderson also told the hearing that while he was unaware that it was against the Rules of Racing to give a horse anything but normal feed and water on the day of a race, "someone was aware of the fact that it shouldn't have been done on the day" because the injection was not listed in the yard's records.

He suggested that this might have been Tom Symonds, his assistant trainer, who did not give evidence to the BHA hearing into the case, but is expected to appear before the RCVS panel later this week.

Henderson said in evidence yesterday that he first realised that TA was a banned substance when he received a letter from the BHA informing him of the positive test. "I was very surprised," he said. "I didn't think we had administered anything terribly illegal and the horse [which finished sixth] had not exactly won the race. I was a bit disappointed with the whole scenario. I couldn't believe it was going to lead to what it has led to. The horse hadn't won, so it couldn't be disqualified."

The hearing heard extracts from transcripts of both the British Horseracing Authority's hearing into the case, which Main refused to attend, and an interview between Henderson and BHA investigators shortly after the positive test had been confirmed.

The RCVS's disciplinary committee heard that Henderson had told the BHA in the summer of 2009 "all I wanted [Moonlit Path] to do [at Huntingdon] was to have a nice time". He also told the Authority's investigators that he was "not aware that it [TA] was detectable", and that "no one ever said to me, Christ, you mustn't use this."

He added that he had "absolutely no motive" to try to improve Moonlit Path's performance at Huntingdon.

"It was the first run of her life at the age of six," Henderson said. "She had shown no natural ability at home and I would have been delighted if she had just completed.

"We start nearly all of our horses in bumpers, which are two-mile flat races for horses that have not run before, and the one simple reason that she hadn't run in a bumper was that she was too slow. So we found her a nice mares-only race over two-and-a-half miles at Huntingdon, and we had another in the race ridden by our first jockey. There was simply not a great deal of incentive for me to want her to go faster."

Henderson told the hearing that in his opinion, Main "is a very good vet", and agreed with Coonan that Main had never suggested that he should do anything to "get around the rules wrongly".

The one issue about the affair that still upsets him, he said, is the use of the word "doping" in connection with the events.

"That really upsets me," Henderson said. "The horse was not doped. She was given a drug for her own benefit."

Henderson was discharged as a witness at the close of Tuesday's proceedings. The hearing is due to continue on Wednesday.

06/24/2011 3:24PM
Daily Racing Form

Outlawing Lasix won't stop the bleeding

By Steven Crist

Reasonable people can disagree about whether the raceday administration of Lasix should be continued, modified or phased out in American racing, but two aspects of the current debate about it simply don't pass the smell test.

The first is the proposition that Lasix is a major issue in the declining popularity of the sport and a significant factor in the industry's current business woes. The oft-repeated narrative is that lifelong horseplayers are suddenly so troubled by Lasix, decades after its introduction, that they are deserting the game, and that newcomers who would otherwise be filling the grandstands are staying home because they are so repelled by it.

No sale. Of course if you poll civilians about whether racing (or water polo, or your local crafts fair) would be better off without "performance-enhancing" drugs, they will answer in the affirmative. From personal experience, however, I see no evidence that this translates to Lasix keeping anyone away from racing. Over the last decade, I have conducted over 100 question-and-answer seminars with tens of thousands of fans and players at tracks and betting parlors across the country. The next one I meet who thinks Lasix is a major issue, or a reason not to play the races, will be the first. Customers are not shy about voicing numerous complaints about the game, but in my experience Lasix is not even on their radar.

They care about illegal drugs and whether the game is on the level, but this has no connection whatsoever to raceday Lasix shots, at least until the general news media swoops in and muddles these entirely separate matters. The dispensation of Lasix is one of the very few things in racing that seems to work pretty well and without controversy or suggestions of impropriety. The public is reliably informed which horses (i.e., just about all of them) are getting it, and which ones are getting it for the first time. There are plenty of things that horseplayers are justifiably disgruntled about – high takeout, unappealing races, poor technology, subpar facilities – but raceday Lasix never turns up on the long list of customer complaints.

The whole issue of whether Lasix can mask other drugs was a valid concern a generation ago – perhaps the best reason to oppose its use – but from all veterinary accounts this is now a non-issue. The vastly increased precision of testing, and a greater reliance on plasma rather than urine tests, has made this a moot point.

There are other reasons to be skeptical about whether it has been a beneficial addition to the sport, such as its possible long-term effect on breeding stock and whether the United States should be so out of sync with other major racing jurisdictions. Customer acquisition and retention, however, are not among them.

The other part of the debate that rings hollow is the disconnect between the words and deeds of some of the most forceful opponents of Lasix – a group of high-minded owners and breeders who say it is detrimental to racing and horses and that the feds must be called in to stop it. The problem is that every one of them continues to give Lasix to their own horses, saying it is unreasonable for them to fight the battles of the turf with one hand tied behind their backs. They say they will continue to give all of their own horses Lasix until the day it is banned because they don't want to give up a competitive advantage.

If this issue ever makes it to the level of Congressional inquiry, racing will be laughed out of the hearing rooms. Those who race their horses on Lasix while decrying its use will unfairly but understandably be perceived as hypocrites whose sense of morality and animal welfare ends the moment it interferes with their personal pursuit of trophies and purses. Those who opine that Lasix is terrible for racing and its horses would have a lot more credibility if they stopped using it tomorrow instead of advocating positions they refuse to adopt for their own horses.

It also would be a lot easier to accept the supposed scorn of the international racing community if a single one of the powerful international stables that sends horses to the Triple Crown and the Breeders' Cup declined to use Lasix as a matter of principle once they get here. Instead, virtually all of them use it while continuing to criticize American racing for allowing them to do so.

If you think racing has an image problem now, just wait until these advocates go to Capitol Hill and tell legislators that Lasix must be banned to save racing and that there are better ways to treat pulmonary bleeding – but that they refuse to ban it within their own stables or even try to embrace any of these supposedly superior treatments.

07/07/2011 11:42AM

Q&A: Mark Johnston

Published on *Daily Racing Form* (http://drf.com)

By Glenye Cain Oakford

Dan Abraham

British trainer Mark Johnston qualified and practiced as a veterinarian before taking out his trainer's license in 1987. From his base in Yorkshire, he has trained the winners of the 1000 and 2000 Guineas, Ascot Gold Cup, and Goodwood Cup, among other prestigious races. Most recently, he won a pair of stakes at Royal Ascot: the Group 3 Queen's Vase with Namibian and the Duke of Edinburgh Stakes with Fox Hunt. Both were purchases from Tattersalls in England, but Johnston shops regularly at U.S. yearling auctions, too. DRF *spoke with him about comments at last month's medication summit in New York that suggested U.S.-bred horses are becoming less popular with British and European buyers because of the United States' relatively liberal medication policies.*

Birthdate: Oct. 10, 1959

Family: wife Deirdre, who also is his assistant trainer; sons Charlie and Angus.

Training base: Kingsley House, Middleham, Yorkshire, England

In your experience, are European buyers losing interest in purchasing American-bred horses because U.S. horses are allowed to run on medications, whereas European horses aren't? For me, one of the great appeals of buying American-bred yearlings was I would buy them on spec, put them out on my website, and they would be sold far easier than Europeans. This year, I bought three, and I took a long time to sell one of them. So it seems to me to have gotten a whole lot more difficult. But even if it is the case that there is less interest, I'm not convinced that it's directly related to medication.

A lot of it could be simply fashion and the fact that you don't have the sexy stallions that raced in Europe and then went on to be world champions, like Storm Bird, Storm Cat, and obviously the Northern Dancer-line stallions. Those were horses who had horses that raced in Europe and then went to stand in the States. Everybody [in Europe] knew them as champions, and if we buy a Storm Cat it sells straight away. You don't have those big names anymore that are so well known in Europe.

The other factor, I am a little bit concerned that they are less sound. But again, I wouldn't be totally convinced that that's down to medication. I think it takes a long time before allowing horses to race on medication comes through as a weakening of the breed.

I have a theory on it, which is no more than a theory. If you look back at the traditional Kentucky-bred, I marveled when I first came to Kentucky and looked at the farms. You have paddocks that are as big as our farms. You have 10 or 20 yearlings out in a 50-acre paddock, where we'd have a 50-acre farm. So American horses were renowned for being tough. I put that down not to the breed, but more to the rearing. They're out there in large groups, galloping around paddocks. I worry that such a huge percentage of yearlings coming to the sales now have had surgery at some stage. Not only am I concerned that that surgery is detrimental to the horse, but I am even more concerned that the time that horse spent in a box when it should have been running around a paddock is far more detrimental than the surgery or not having the surgery at all. Frankly, I don't like surgery full stop. I read somewhere that X number of weeks in the box as a foal basically finished a racehorse. I'm not sure what the figures are and I'm not sure whether it's true, but I can imagine it, and that would worry me terribly. But I also just don't think we should be correcting minor deformities of the foal. I think that's more likely to slow a horse down than speed it up.

In the years since you've been shopping for horses in the States, have you seen a noticeable drop in soundness? I don't particularly feel I've seen a drop-off in soundness. But as long as I've been coming to the sales, maybe 12 years or so, the X-rays and the surgery have been popular throughout that time. It's more a case of comparing over the last 10 years, the soundness of the American-breds versus the European purchases. It seems to me that the Europeans are sounder.

I don't know that racehorses are getting less sound overall, and that's another thing that is hard to evaluate, because we race them harder. People always talk about how sound they were 50 years ago, but they didn't have the same pressures on them, and they didn't go as fast. People like to be nostalgic and say the Secretariats and so on went faster than the horses of today, but the fact is, they didn't. And they weren't under the same pressure. If you put those horses under more

pressure, you'd get more injuries. We're also so much better at diagnosing things now, and that's possibly to the detriment, as well. We're always finding problems with horses today.

Trainer John Gosden, based for years in California and now back in England training, recently was quoted as saying there's a perception that American-bred horses are tougher in that they will "play through the pain." Is that true in your experience? I have no evidence for that. I appear to have more niggling soundness problems with my U.S.-bred horses. Whether that's a true soundness problem or an inability to "play through the pain," I'm not sure.

Are your concerns about these issues affecting your buying habits in the United States now? A little bit, but I think my buying habits are under a bit of pressure anyway, no matter where I'm buying horses. I'm struggling to sell horses. The recession has hit pretty hard, and it's hard to find owners. So it's much more difficult to buy horses on spec. Obviously, there's a bit more risk involved when we're buying them on the other side of the Atlantic and have to ship them home and all that.

Are you still planning to come to the U.S. yearling sales this year? Absolutely. I wouldn't miss it for the world. I still love to come. I love to see so many horses in one place. And even if you don't have the sexy stallions that we knew just a few years ago, they'll come again, I'm sure. It's just such a big market, you can't not be involved. The horses are so well presented, and you can see so many in a short space of time, I love to be involved.

On a lighter note, what horse in history do you wish you had trained? Sea the Stars. I'm not a great believer that horses of yesteryear were better than horses of recent years. I think Sea the Stars is the best horse I've ever seen. In its generation, Nijinsky or Brigadier Gerard – well, no, it would still be Sea the Stars. I think he's better than them. He was a complete superstar.

INSIGHTS

SEPTEMBER 16, 2011

by Dick Powell

I have the pleasure and luxury of attending just about every horse racing conference held in the United States. Clients of my consulting business send me to every HBPA event, RCI, International Simulcast Conference, University of Arizona Symposium on Racing, Albany Law School Racing Conference and New York Gaming Summit. I attend all the sessions even though some of them do not directly affect what I do.

One topic that many of these conferences have covered is race day medication. I have sat through numerous panels discussing medication issues and have learned a lot.

For years, I was against Lasix being allowed on the day of the race. Back in 1994, I was still a consultant for the New York Racing Association (NYRA) reporting directly to the president. When Gerry McKeon retired and was replaced by Kenny Noe, my days were numbered. Being an adviser to Kenny Noe was like being a deckhand on a submarine. I'm not saying Kenny didn't listen to his staff but his idea of a suggestion box was a paper shredder.

So one night at dinner the subject of Lasix came up and Kenny was adamant about changing NYRA's stance against its use on race days. His point was how can the rest of the country be wrong and NYRA be right? We discussed the pros and cons of legalizing it and I came down on the side of keeping the policy of banning it. Big mistake; at least, for me.

But as time has gone by and I have not only had the luxury of attending conference sessions on the topic but having numerous discussions with many horsemen and veterinarians, my stance has changed.

Exercised induced pulmonary hemorrhaging (EIPH) is what happens when capillaries burst in a horse's pulmonary system. At best, the blood from the hemorrhaging is insignificant and has no effect on the horse's performance. At worst, it can result in sudden death to the horse and not every horse that dies from it has visible evidence of the bleeding coming out of its nostrils. In between, the severity varies. Nearly all horses racing suffer from it in some form.

Just about all horses performing in any form suffer from EIPH. Quarter Horses, Standardbreds, barrel racers, etc. suffer from it in addition to Thoroughbreds. What makes Thoroughbred racing different is how it is anaerobic in nature, meaning the horse goes into oxygen debt for lengthy periods at the end of the race. Anyone that has ever run a 400-meter race on track knows the feeling. Running hard for long periods of time results in lactic acid being secreted and muscles tying up. We used to call it rigor mortis.

Not only is the Thoroughbred asked to go into major oxygen debt but often times has to do it in bad air quality. Throw in heat and humidity and you have all the ingredients of asking horses to do things that border on being inhumane.

Lasix can relieve the symptoms of EIPH in most horses. Considering the positive therapeutic effects, it's hard to understand that it has become the source of controversy that it is.

I used to think that giving two-year-olds Lasix was a big mistake and that all two-year-old racing should be devoid of it to see who the best horses are. However, I learned that the earlier you treat horses with Lasix, the less permanent damage is done to their lungs.

Lasix, because of its effect of being a diuretic, used to be used as a "masking agent" for other drugs. But, what everyone seems to agree upon is that today's sophisticated drug tests are good enough to detect the banned medications whether Lasix is being used or not.

The rest of the world bans Lasix so why don't we? All of the United States, Canada, most of south America and Saudi Arabia allow race-day Lasix. While that is still a minority, the fact is that the entire racing world with the exception of Hong Kong and Singapore allow horses to train on it.

In conversations with many people that have international experience, there is a feeling that the drug testing that other jurisdictions brag about are not up to our standards. They test urine, not plasma, and they have high thresholds that trigger a positive. Adjunct medications are allowed and one trainer told me he would love to take samples of international horses and run them through our testing procedures to see who is really "clean."

We all bemoan the drop in average starts per season in America. Many blame it on our addictions to race-day medications. Yet, the data shows that the entire racing world has seen the average number of starts per starter each year has dropped.

Twenty years ago, the United States was third in annual starts per starter. Japan was number one and Italy was number two. Now, Japan is still number one, even though their average starts per starter each year has dropped, South Africa is number two and the United States is still number three. How can that be? That's not what we hear from the Lasix opponents but the statistics are from the International Federation of Horseracing Authorities (IFHA).

Steroids were banned from most jurisdictions a few years ago. While that may have been the right thing to do, we haven't seen a jump in starters since it went into effect. Will we see a jump in starts per starter if we ban Lasix? I sincerely doubt it as you are removing a therapeutic medication that keeps horses racing.

As a bettor, we have all had to adjust to the presence of Lasix. First time Lasix can be a powerful indication of expected improvement. Sometimes second time Lasix is a big move since we don't really know how big the dosage was the first time. For me as a bettor, I don't want it to be a factor at all. But rather than ban it, I think we should mandate it.

Nearly all Thoroughbred race horses bleed. If you think we can breed our way out of this by separating the horses that bleed from those that don't and breed a new racehorse that doesn't bleed and doesn't need Lasix, you would have to ban it in training as well which nobody wants to do.

And, how do you explain banning it to the animal rights activists that view our sport as being cruel and inhumane? We went nuts after Eight Belles broke down in the 2008 Kentucky Derby (G1). Task forces were formed and racetracks and their maintenance procedures were examined in order to show the general public that we were doing everything we could to protect the horses that are racing.

If we mandated that all horses that are racing be treated with the same dose of Lasix, we take it out of the handicapping equation. We show the general public that we continue to diligently look out for the welfare of the horses that are racing. And we do the right thing by the horse by reducing the severity of EIPH.

What If Zenyatta Was Deprived of Lasix?

In the second part of Patch series, people opposed to the banning of Lasix as a race-day medication, including the great filly's trainer, have their say.

- By Larry Stewart October 14, 2011

There is little question that the best horse racing story of this era, or any era for that matter, was Zenyatta's amazing run of 19 straight victories before barely losing to a horse named Blame in the 2010 Breeders' Cup Classic in Louisville, Ky. During her run, Zenyatta, a filly, had dramatically beaten the boys in the 2009 Breeders' Cup Classic at Santa Anita.

Well, think about this for a moment: If Lasix, the diuretic that helps prevent internal bleeding in racehorses, were banned as a race-day medication, there may never have been a Zenyatta story, as least not that one that captured the nation and put horse racing back on the front page.

Insiders say Zenyatta was a bleeder and needed Lasix. When the filly's trainer, John Shirreffs, was asked about the proposed banning of Lasix as a race-day medication, he said he was "vehemently opposed" to such a ban.

However, when asked specifically about Zenyatta, he declined to go there. "I don't want to single out any one horse, but generally speaking, a ban of Lasix would be a very bad thing."

Jerry Moss, Zenyatta's owner, also skirted the issue. When asked if we would have had the Zenyatta story without Lasix, he said, "I don't now about that." But he does oppose a ban of Lasix as a race-day medication.

"I think if Lasix were made illegal, then trainers and veterinarians would just turn to something else," said Moss, a member of the California Horse Racing Board.

Another CHRB member, vice chairman David Israel, used the same wording as Shirreffs when he was asked about the proposed ban. "I am vehemently opposed," he said.

Keith Brackpool, the CHRB chairman, declined to give his personal viewpoint but did say, "It is going to be a very interesting debate."

This is the second part of a two-part series on that debate. The first part examined the argument for banning Lasix, which has been proposed but some organizations and prominent people in horse racing. But most of the people interviewed by Patch during a one-month investigation were outspoken in opposing such a ban.

"It's ludicrous," said 71-year-old veteran trainer Kathy Walsh. "Lasix is a preventative that 85% of the horses need to prevent bleeding. The people who are pushing for this ban are misinformed."

Trainer Darrell Vienna said, "It would be a huge mistake to ban Lasix. Calling Lasix a performance-enhancing drug shows these people don't know what they are talking about. The exact opposite is true. These people are ignorant about this topic."

Trainer Bob Baffert is another strong opponent of the proposed ban.

"When I first got into racing in Arizona, I wasn't even aware of Lasix," he said. "I have no idea who many more horses could have raced if they had been given Lasix, but I am sure it was quite a few. I think once a horse shows that it needs Lasix, that horse should be able to get it."

Trainer Bruce Headley said, "It would be like banning aspirins for humans. We take aspirin when we get a headache, and that is a good thing. A horse needs Lasix if he is a bleeder."

Hall of Fame jockey Eddie Delahoussaye said, "I raced before Lasix was around and I raced after it became a legal medication. We're a lot better off with it than without it, I'll tell you that for sure. In the old days horses that bled a lot couldn't race and I don't know what became of them.

"I was in Kentucky recently and talked with Dr. Rob Holland, one of the leading horse veterinarians in the country. The way he explained to me, I was convinced that Lasix is a preventative diuretic, not a steroid or performance-enhancing drug of any kind. I think there are a lot of misinformed people dealing with this issue."

Most private veterinarians are against the proposed ban because administering Lasix puts money in their pockets.

But Patch interviewed two veterinarians who are in regulatory positions, Rick Arthur and Dana Stead.

Arthur, the medical director for the CHRB, said, "I think horse racing could survive, even thrive, without Lasix. But there clearly is no consensus here and I think it is going to take multiple generations of horsemen learning to manage horses that bleed rather than giving them Lasix before we reach any kind of consensus."

Stead, a track veterinarian working the Southern California circuit, said, "I would like to eventually see a ban but it's not something that is going to happen over night. We're not going to have Lasix on Dec. 31 and then not have it on Jan. 1."

One retired trainer who asked not to have his name used got into a discussion with this reporter and former jockey Alex Maze about this issue. The retired trainer said he got out of horse racing because of drugs and is opposed to drugs of any kind.

Maze told him that banning Lasix, in addition to putting horses and the jockeys on top of them at risk, would also decrease field sizes and that would impact the sport as a whole.

"Now there is one argument that has me rethinking this issue a little," the retired trainer said. "The one thing that could hurt horse racing more than anything is a lack of horses, and I would hate to see that."

op/ed feedback

CLARA FENGER, DVM, PhD, DACVIM

In a recent Op/Ed piece by Dr. Gregory Ferraro (click here), two recent papers were discussed, and Dr. Ferraro's conclusions are simply that they "provide serious evidence that the use of race day Lasix is neither necessary nor prudent." In fact, the very papers cited by Dr. Ferraro argue the opposite point.

SA Preston's Hong Kong EIPH paper:

First, the Hong Kong study, conducted by S. A. Preston, et al. has so many errors, including simple arithmetical errors, that any conclusions made by the authors must be treated with great caution. In this paper, Preston, et al. reported on the racing careers of 822, [or possibly 924], horses imported for racing between 2007 and 2012. In one section of the paper, she states that a total of 822 geldings were imported to Hong Kong, but in a critical table [table 2] in the paper, the numbers add up to 924. She also claimed that 405 out of 732 were EIPH+, and 326 out of 732 were EIPH-, which actually adds up to 731, not 732. The numbers are equally curious in Table 2 where the total number of horses that never bled is 157, not 326, as stated in the text. Figure 1 is a simple pie chart, expected to add up to 100%, but in Dr. Preston's paper, adds up to 115%. So, it appears that the horses are grouped differently in different parts of the paper, with no explanation throughout the text. These examples are only a few of the numerical and statistical inconsistencies in the paper, which result in the paper being almost incomprehensible and of questionable scientific value.

The authors suggest that the Hong Kong horses race longer than horses in the U.S. However, she is comparing Hong Kong geldings with EIPH (18 lifetime starts) to all U.S. horses, regardless of EIPH status and regardless of gender (colts, fillies, geldings: 16 lifetime starts). There is no question that, if she were to compare apples to apples instead of apples to oranges, the statistics would have come out exactly opposite of her assessment.

When the number of lifetime starts for all of the groups of Hong Kong geldings are considered, it appears to be closer to 15, and the number of lifetime starts for U.S. geldings is likely to be in the 20s (because well-bred colts and fillies often retire early to the breeding shed). One thing that is clear from the Preston paper: about a quarter of the horses in Hong Kong (21.6%-27.6%, depending upon which numbers are correct in the paper) were retired as a result of EIPH. This number is so high, that we, in the U.S., would consider it to be an unacceptable animal welfare issue. Dr. Ferraro concludes that the most important finding in this paper is that EIPH+ horses had longer careers and more starts. In fact, The 405 EIPH+ horses bled at least once out of about 15 endoscopies. The 326 (maybe?) EIPH- horses did not bleed once out of about nine9 endoscopies. It is quite possible, and even probable that some of the EIPH-horses bled at a time when they were not scoped (maybe EIPH would have been identified in at least one of six more endoscopies?), since there was no regular planned endoscopy in place (another critical shortcoming with this paper). The results show this phenomenon well: the longer a horse raced, the more likely he was to have more endoscopies, and the more likely he was to be diagnosed with EIPH. So, Dr. Preston showed only that the more times you scope a horse, the more likely you are to diagnose EIPH. Since previous studies have shown that if you scope horses often enough, they will all be diagnosed with EIPH, this information is hardly new.

In the Hong Kong study, 4% of the total number of horses experienced epistaxis, a number which is considerably higher than found in other previously published studies, which range from 0.15% to 2.41%. Prior to the widespread use of Lasix in this country, 82% of the horses that died suddenly on the racetrack died from pulmonary bleeding. Since the widespread use of Lasix, this phenomenon is almost unheard of. In fact, the most elegant and robust study ever performed to study the effect of Lasix on EIPH was the Hinchcliff, et al study, which showed unequivocally that study horses treated with Lasix never bled a grade 3 or 4…which would be the level of EIPH where you may expect the horse to progress to epistaxis and where there is risk of sudden death. Additionally, a 10-year study of racing fatalities in Victoria, Australia, where Lasix is banned, showed an exceptionally high rate of sudden death at that racetrack, further supporting the humane and appropriate use of Lasix to prevent EIPH. At a time when racing is struggling to build up its fan base, more dead horses on the track like those seen in Australia is hardly the way to do it.

In Dr. Ferraro's opinion, this paper lays aside the argument that the use of race day Lasix is necessary to protect the health and welfare of race horses, while in fact, the data argue the opposite. While many horses are not harmed over time by the presence of post-race or training EIPH in the Preston study, most horses that bled a grade 3 or 4 first bled a grade 1 or 2, and horses that experienced epistaxis first bled a grade 3 or 4.

Cont. p11

Since we know from the South African study that Lasix prevents most grade 3 or 4 EIPH, the need for Lasix becomes more urgent as a result of the finding of the Hong Kong paper. Certainly, we do not want 4% of our horses to bleed from the nose, like they do in Hong Kong, when a simple, safe and effective preventative, Lasix, will prevent this severe pathological condition which requires serious medical treatment and extended rest.

BD Velie's Australian EIPH study:

The second research investigation mentioned by Dr. Ferraro was conducted by B.D. Velie, et al, involved a 10-year study of 117,088 horses corresponding to a remarkable 1,852,912 individual performance records of Australian race horses, again a study conducted in a country that does not permit the use of race day Lasix. This study was interested in determining if there was a genetic predisposition for epistaxis and therefore, studied the pedigrees of 715 sires and 2351 dams. As a result of this investigation the researchers were able to demonstrate that "a significant proportion of the variation in epistaxis phenotype is attributable to the additive genetic variation in the population." In other words, in the researcher's opinion, "the genetic composition of a horse clearly contributes to the likelihood of its experiencing epistaxis." In fact, this finding is not new: the heritability of epistaxis was determined to be 0.3-.55 in a South African group of horses. However, do not confuse heritability with a direct genetic contribution. Heritability means that there is a relationship between a trait and certain bloodlines and is a unique feature of the specific population studied. Heritability does not indicate that there is a specific genetic defect that causes the expression of the trait.

A genetic principle called negative selection clearly calls into question the idea that EIPH is a specific genetic defect. If a trait has only a negative effect, it will be eliminated from the population within a few generations. Both heritability studies were performed in countries in which no Lasix is permitted. Hence, if there were a "bleeder gene" it should have been eliminated from the population forthwith. And yet they continue to bleed. Most likely, EIPH is associated with some other trait, and likely a trait for which we positively select racehorses. The cause of EIPH is the incredibly high pulmonary blood pressures which are experienced during maximal effort, as huge volumes of blood are transported both to the muscles and through the lungs. It is likely that as we select racehorses for excellence in their maximal effort, and the ability to transport huge volumes of blood at high speed, we are similarly selecting them for EIPH.

Hence, the heritability of EIPH is hardly a "genetic susceptibility to this condition," but rather an unintended consequence of breeding for speed. Fast horse = high pulmonary blood pressure. In reality, American horses and bloodlines continue to excel throughout the world.

It is most likely that our continued use of a safe, effective and humane preventative for EIPH, Lasix, actually allows exceptional individuals (like Northern Dancer, a legendary bleeder) to remain in the gene pool, and permitting the type of genetic diversity required for healthy, long-term survival of the breed. Additionally, both the Velie and Weideman papers agree that 50-70% of the cause of EIPH is from non-inherited sources. The best possible stewardship of horses includes the reduction/prevention of EIPH by doing such things as minimizing dust and pollution in the barn areas and use of a safe and effective preventative--Lasix.

I strongly encourage anyone wanting to understand this issue not to blindly accept the conclusions of studies, but to actually critically read the papers themselves and draw their own conclusions. They will see an entirely different story. The Preston and Velie studies create more questions than they answer, but they do provide serious evidence that the use of race day Lasix is both necessary and prudent.

Dr. Clara Fenger graduated with her veterinary degree from the University of California at Davis in 1988, and after briefly practicing in California, she went on to an Internal Medicine residency and Master's Degree program in Equine Exercise Physiology at the Ohio State University, where she studied under the tutelage of Ken McKeever and Ken Hinchcliff. She later received her PhD studying Equine Protozoal Myeloencephalitis at the University of Kentucky. During her graduate studies at UK, she also worked for the Kentucky Racing Commission as a State Veterinarian and developed a passion for the sport of horse racing. She continued this association with the racing commission for 15 years. She is currently a practitioner in Central Kentucky specializing in both Thoroughbreds and Standardbreds, and owns Thoroughbred racehorses.

op/ed
by jerry brown

AN IMMODEST PROPOSAL

In comments in the *TDN* this week, both Dr. Larry Bramlage and Arthur Hancock took the position that Lasix needs to be banned because bettors want that to happen, and handle will suffer if we don't (click here). Those gentlemen are certainly qualified to comment as professionals about veterinary medicine and breeding, but when it comes to bettors and handle, they are playing in my ballpark. My handle is seven figures a year, and I produce high end handicapping data used by hundreds of big bettors, including some who bet more than I do. And that idea isn't just untrue, it's dangerously wrong. Dr. Bramlage says "the general public doesn't understand" Lasix. I don't know whether families picnicking at Saratoga understand Lasix or not, but I do know those people don't drive handle. Allen Gutterman once estimated that 2% of those betting are responsible for 50% of handle, and my guess is that 10% of us generate close to 90%. We are not passive "fans"--we are horseplayers, participants in the industry. And I can tell you for a fact that we make it our business to understand Lasix as it applies to handicapping, and that not a single horseplayer I have talked to will bet MORE if Lasix is banned. It would add an extra unhandicappable variable to each horse in every race, and more confusion. Some of us--like me--would bet less.

People bet when they have an opinion. The stronger the opinion, the more likely they are to bet, and the more money they will bet. Things that create uncertainty hinder investment in business, and the same applies here as well. Not knowing whether the reason a horse stopped last time was because he bled, and whether the problem has since been dealt with, creates uncertainty. Factoring in the randomness that someone in the field will bleed today, at a short price, creates uncertainty.

It's worth thinking about why Lasix is the only drug that is listed in the program. And it's worth thinking about how people would pay for and bet on the basis of inside information that would become crucial if Lasix is banned, and how that would affect public perception. It's happening now with illegal drugs, and it has destroyed the morale and enthusiasm of many horseplayers. I see it all the time on the board at my website. It's also worth thinking about something that happened a few years ago, when the industry went tearing off to build synthetic tracks, without talking to those of us who were going to have to try to answer undecipherable questions about how each individual horse was going to handle each surface, and make decisions about betting those races (or not).

Is everyone happy about how that worked out?

There are two major problems with the drug debate that is currently going on in our industry. The first is that the Lasix issue is being lumped in with the illegal drug issue, because both involve drugs, and in some cases because people have agendas. I've been heavily involved in trying to stop cheating in our game for a long time, not for idealistic reasons, but because money is being stolen from honest horsemen and horseplayers (like yours truly). Attempting to stop something illegal, which everyone agrees about, and attaching it to banning a legal therapeutic drug, which is controversial, is like having a bill to fix the Veterans Administration, and combining it with declaring war on Iran, because both involve the army. As long as it's both or none, movement will be impossible on the non-controversial part, the relatively low hanging fruit.

The second problem is that only two alternatives are being discussed regarding Lasix, and that's a false choice. It's not simply they all get to run on it, or none do. So here's a rational, pragmatic proposal to deal with Lasix. Not as a sports issue, but as a business issue--because this is a business first, and a sport second. If you don't think so, try it without bettors.

First of all, starting with next year's 2-year-old crop, we go back to the way it used to be--to get on Lasix a horse has to be certified as a bleeder by a state vet, not your own vet, following a race or work.

Op Ed cont. p8

Op Ed cont.

Second, any horse who goes on Lasix has to carry a five-pound penalty. From what work I've been able to do on this with very little data that looks about right, but after a year there will be lots of data, and the penalty can be tinkered with. Third, older horses currently on Lasix have the option of staying on it--and accepting the five-pound penalty.

The idea is to allow the horses that really need medicine to get it, and to remove the incentive for others to use it. Best guess is this will drastically reduce the number of horses on Lasix over time, and enable us to concentrate on real problems, like the fact that nasal strip info is not being provided to the betting public, which is ridiculous. And oh yeah, the minor problem we have with illegal drugs--which is killing our industry.

Jerry Brown is the president of Thoro-Graph Inc. (www.thorograph.com) publisher of data used by professional horseplayers and horsemen. As a consultant, he is responsible for the purchase of 87 stakes winners including Victory Gallop, Distorted Humor, and Rachel Alexandra.

Lasix use is in best interest of horses

By Rick Violette Jr., Commentary
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> Unlike amateur, professional and Olympic sports, which ban specified substances in competition while allowing a laundry list of medications that includes everything from pain killers to sedatives to muscle relaxers, horse racing bans every single medication on race day except furosemide, commonly known as Lasix.

Why do we permit racehorses to be treated with Lasix? Lasix protects a horse's lungs from exercise-induced pulmonary hemorrhage, a physiological reaction to strenuous exercise that affects not only the majority of thoroughbred racehorses around the world, but equine athletes of many breeds that compete in harness racing, barrel racing, eventing and polo, as outlined in the Merck Veterinary Manual.

The Journal of the American Veterinary Medical Association published the results of a study on the effectiveness of Lasix in alleviating the condition in 2009. The study, underwritten in part by The Jockey Club, concluded that the pre-race administration of Lasix decreased the incidence and severity of such hemorrhaging. Dr. Anthony Verderosa, chief examining veterinarian for the New York Racing Association, reported that episodes of epistaxis, the most severe form of this condition — when a horse is in crisis and bleeding from the nostrils — was reduced nearly 80 percent in New York after Lasix was legalized in 1995.

Science tells us that horses suffer from exercise-induced pulmonary hemorrhage, and Lasix is the only truly effective treatment currently available. That is why the New York Thoroughbred Horsemen's Association, representing the 5,000-plus owners and trainers competing at NYRA tracks, is staunchly opposed to any ban on this therapeutic medication.

Lasix is in the best interest of horses cont.

Opposition to a ban on Lasix does not, however, signify opposition to medication reform. New York's horsemen backed the ban on anabolic steroids enacted in 2009. The horsemen's association underlined that support when spending $415,080 to buy the equipment needed to test for steroids.

The association is a catalyst behind the national Uniform Medication Program, which mandates strict guidelines for therapeutic medications approved for use in training and for the accreditation of testing labs. The association is an advocate of the "multiple medication violation penalty system," which ensures the punishment of repeat offenders.

New York's horsemen are behind any initiative that emphasizes the welfare of the horse. The horse is not the top priority in anti-Lasix arguments, which focus on fan perception, and pressure from the international racing community.

There is debate on whether or not Lasix is a performance-enhancer, whether it will weaken the breed (an argument countered by Dr. Hiram Polk Jr. in his case study, "North American Pedigrees Down Under," which demonstrated that horses with North American bloodlines raced more frequently and needed less time between races than those with Australian pedigrees).

A ban on Lasix will not eliminate exercise-induced pulmonary hemorrhage, it will only eliminate the best protection we have against it. The answer to "Why Lasix?" is simple: We are obligated to doing everything possible to protect our horses.

The author is president of the New York Thoroughbred Horsemen's Association.

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RECENT RESEARCH ON EIPH AND BLEEDING

Push Lasix To 24 Hours Pre-Race? Study Says 'Hold Your Horses'

by Natalie Voss | 01.29.2018 | 3:19pm

As the debate about race-day medication rages on, hay/oats/water advocates have pushed to eliminate furosemide from the American raceday. But researchers and veterinarians have been left wondering: Will furosemide (widely known as Lasix or Salix) work as well to control exercise-induced pulmonary hemorrhage (EIPH) if it's given the day before a race?

According to a pair of recent studies presented at the 2017 American Association of Equine Practitioners Convention in San Antonio, the science (for now) says no.

Currently, furosemide may be given up to four hours out from race time. Dr. Heather Knych and a team of researchers at the University of California wondered whether a dose 24 hours from race time would be equally good at stopping bleeding.

Knych and her team dosed 15 horses with either saline or 250 mg of furosemide. One group was given its dose four hours prior to a simulated five-furlong race; the other 24 hours before. The team collected blood samples before and after the simulated race and performed an endoscopic exam and a bronchoalveolar lavage (BAL) after the race. They then assigned the horses EIPH scores based on the diagnostic results. All horses received each treatment with a resting period of two weeks in between so researchers could understand how the same individual reacted under different protocols.

The researchers found there was a statistically significant difference in scores between the four-hour and 24-hour furosemide groups. Knych said 93 percent of horses receiving furosemide four hours before their runs were rated as Grade 0

for bleeding, while 60 percent of horses got a Grade 0 when given furosemide 24 hours out. All horses had some red blood cells in their lung lavages.

Grade 0 horses were those which showed no signs of blood on endoscopic exam. Grades range from 0 to 4.

Knych pointed out that the horses' history regarding EIPH wasn't known to researchers before they entered the study and it's possible selecting specifically for known bleeders might have made a difference in the results. Based on the final times of individual runners, Knych noticed there was a significant range of athletic ability within the group of 15 horses, which also may have impacted results.

Still, Knych doesn't think the results will exactly have regulators rushing to push the furosemide administration time to 24 hours pre-race.

"We did not see a significant reduction in either endoscopic or BAL red blood cell counts with 24 hours furosemide. By those criteria, this study did not support 24-hour furosemide as being effective," she said.

As we reported in late 2017, experts view EIPH as a somewhat unpredictable condition – a horse's having bled once doesn't necessarily mean he will bleed every time he runs or that he will bleed enough to limit his performance. While this study wasn't designed to examine that problem, Knych said it did raise an interesting question for her.

"There are numerous studies looking at endoscopic EIPH prevalence. Our horses were a very healthy group. They had lower than expected EIPH scores, but all had (red blood cells) in their BAL's post-work, even the four hour furosemide runs," said Knych. "Horses raced for centuries without furosemide and still do in many parts of the world. The unanswered question is whether U.S. horses racing with furosemide are healthier than horses racing internationally without furosemide. That study has not been done and would be hard to design."

Could alternative management options work?

Also at the 2017 AAEP convention, Dr. Warwick Bayly of Washington State University presented the results of his study into prophylactic EIPH treatments. Since furosemide works by reducing blood pressure in the pulmonary artery through fluid

loss, Bayly wanted to know if controlling a horse's water intake could produce a similar result. Bayly and his team gave six horses different doses of furosemide with and without controlled access to water 24 hours before a treadmill workout. The horses had BALs and were scoped after exercise.

Bayly found the combination of .5 mg/kg of furosemide (the lower of two doses he used), combined with controlled water access significantly reduced severity of EIPH compared to any other combination of furosemide dose and water control. Why did the lower dose with limited water do better than the higher dose? It's hard to say, but Bayly guesses it may have reached a 'sweet spot' in keeping blood pressure in the pulmonary artery low while allowing the horse a better overall hydration level.

How do trainers implement water control into their pre-race regimens? We don't yet have enough information to say for sure. Finding that 'sweet spot' for any individual horse can be tricky on a practical level and this study only provides a piece of the puzzle.

"There's definitely going to be individual differences. You can count on that," said Bayly. "There was no question we only had six horses but there were differences in response amongst those horses.

"The other thing that's important is EIPH is a very complex condition. We have data from these horses on the treadmill and when they've been on the racetrack, breezing or doing simulated racing when they had no drugs or no treatment. Even then, there's considerable variation from exercise bout to exercise bout, especially on the track. On the racetrack, from a half mile on up, severity of the bleeding in all cases was a lot more severe than on the treadmill. That raises a number of questions with respect to research that might be done in the future and with respect to research that's been done in the past."

Bayly admitted the sample size of six horses was too small to draw any broad conclusions. This was actually a follow-up study to one he had done earlier with four horses, in which he got a remarkably different result.

"It's rare, that in the world of scientific endeavor, you work out everything you want to know about a question in one experiment," he said. "You go through a series of them, you get some data, you analyze that, you interpret it, and based on that

you decide what to do next. This is just a good example. Scientific progress is incremental. It's rarely earth-shaking and like Superman jumping over a tall building in a single bound."

Where does that leave trainers who may want to change their pre-race routines to avoid EIPH? Bayly said he's not sure, but he points out past research has shown furosemide doesn't always prevent EIPH in horses who are prone to it (Bayly recalled one study which indicated as many as 30 percent of horses receiving a dose of the drug either got worse EIPH or saw no change in their EIPH scores from when they went without).

"That just underlines that Lasix isn't the panacea and again there's a lot of variation in the extent to which an individual horse will respond to Lasix," said Bayly.

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This entry was posted in NL Article, Ray's Paddock, Vet Topics and tagged Dr. Heather Knych, dr. warwick bayly, drugs in racing, EIPH, EIPH and the Racehorse, furosemide, lasix by Natalie Voss. Bookmark the permalink.

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Effectiveness of furosemide in attenuating exercise-induced pulmonary haemorrhage in horses when administered at 4- and 24-h prior to high-speed training

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Summary

Background: Due to the high prevalence of EIPH in racehorses and its potential impact on the horse's health, furosemide administration is permitted up to 4-h prior to post time in most North American racing jurisdictions. Anecdotal reports suggest that administration of furosemide 24-h prior to strenuous exercise may be equally effective in decreasing the severity of EIPH.
Objectives: To 1) compare the efficacy of furosemide in reducing the presence and severity of EIPH when administered 4- or 24-h prior to strenuous exercise 2) characterise electrolyte and blood parameters following administration of furosemide at 4- and 24-h prior to exercise.
Study design: 3-way crossover.
Methods: Fifteen Thoroughbred racehorses received 5 mL of 0.9% NaCl or 250 mg of furosemide either 4- or 24-h prior to a 5-furlong simulated race. Blood samples were collected prior to and post-run for determination of furosemide, lactate, haemoglobin and electrolyte concentrations. One-hour post-race, an endoscopic exam and bronchoalveolar lavage (BAL) were performed. Horses were assigned an EIPH score based on predetermined criteria and the number of red blood cells in BAL fluid was determined.
Results: Endoscopic EIPH scores were lower in the 4-h vs. the 24-h ($P = 0.03$) furosemide groups. RBC counts in BAL fluid were lower in the 4-h furosemide vs. saline treatment groups ($P = 0.01$) but no difference was noted between the saline and 24-h furosemide groups ($P = 0.3$), nor between the 4- and 24-h groups ($P = 0.5$).
Main limitations: Small sample size and large range of running times for the 5-furlong work.
Conclusions: While none of the treatments prevented EIPH, endoscopic scores and RBC counts in BAL fluid support the efficacy of furosemide in reducing the severity of EIPH. Endoscopic scores were lower in the 4-h furosemide group compared with 24-h administration. Red blood cell counts were lower in the 4-h furosemide group compared with saline treatment.

Keywords: horse; furosemide; horse racing; exercise-induced pulmonary haemorrhage; Lasix; bronchoalveolar lavage

Introduction

Exercise-induced pulmonary haemorrhage (EIPH) is a major issue for the racehorse industry with a high occurrence rate reported in both Thoroughbred and Standardbred racehorses [1–3]. Published reports have described the prevalence of blood within the trachea in Thoroughbred racehorses at 43–75% when examined endoscopically within two hours of racing [4–7]. Furthermore, the incidence appears to increase with repeated examinations [7,8].

EIPH is associated with increases in pulmonary arterial, capillary and wedge pressures as a result of strenuous exercise [9]. Currently, there is no effective treatment for EIPH but the diuretic furosemide has proven beneficial as a prophylactic treatment in reducing EIPH scores [4,7]. While its exact mechanism of action in preventing EIPH is unknown, furosemide has been shown to attenuate the increases in pulmonary arterial pressures associated with strenuous exercise [10,11].

Although the diuretic effect of furosemide occurs fairly quickly following administration [12], there appears to be a considerable lag time before changes in pulmonary arterial pressures are observed [13]. Magid *et al.* [13] reported no effects in pulmonary haemodynamics when furosemide was administered 1-h prior to strenuous exercise. Attenuation of exercise-induced pulmonary capillary and venous hypertension were noted when furosemide was administered 2-, 3- and 4-h prior to exercise [13]. Anecdotal reports suggest that administration of furosemide 24-h prior to strenuous exercise may be similarly effective in attenuating the effects of strenuous exercise on pressures and haemodynamics, thereby reducing the severity of EIPH.

Due to the high prevalence of EIPH in racehorses and the potential impact in the short term on athletic performance and over the long term on the horses' health, most North American racing jurisdictions permit furosemide administration as a preventative measure for EIPH up to 4-h prior to post time. Internationally, the use of any medication on race day is prohibited, leading to inconsistencies and ongoing controversies between North American racing jurisdictions and international racing regulatory guidelines. If effectiveness of furosemide given 24-h prior to a race is found not to be inferior to administration 4-h before racing, a change in the administration time of this medication from 4 to 24-h prerace may be warranted.

Previous studies have described the effects of furosemide on EIPH in both field trials and with horses actively in race training [4,7] as well as with horses running on a high-speed treadmill [14]. The objective of the current study was to expand upon these previous studies by assessing the effects of furosemide in attenuating the severity of EIPH in actively racing Thoroughbred horses when administered at 4- and 24-h prior to post time

in simulated races. This goal was accomplished utilising a combination of endoscopic examination of the airways and assessment of RBC counts in bronchoalveolar lavage (BAL) fluid.

Materials and methods

Horses

Fifteen client-owned Thoroughbred horses (eight fillies, six geldings and one intact male, age 2–4 years) were studied. The study was advertised to racetrack practitioners and trainers in Northern and Southern California. Only horses that were in active race training and could be committed to complete all three runs over a 5-week period were enrolled. Investigators had no prior knowledge of a horse's EIPH status at the time of enrolment. Horses were housed at their racetracks and remained under the care of their trainers.

Study design and drug administration

This study was conducted in a randomised, three-way crossover design. Each horse received 5 mL of 0.9% NaCl i.v. 4-h prior to a simulated race, 250 mg (5 mL) of furosemide i.v. 4-h prior to a simulated race, and 250 mg (5 mL) furosemide i.v. 24-h prior to a simulated race. Water was withheld starting immediately after dosing for horses in the 4-h furosemide or saline groups. Horses receiving furosemide 24-h prior to the simulated race received 2.5 L of water every 4-h until 4-h prior to the simulated race, at which time water was withheld. All horses had free access to water following completion of the simulated race. Randomisation and assignment to a treatment group was performed by an investigator who was not involved in drug administration or grading of the endoscopic exams. All horses received all treatments and the order of administrations to each horse was determined using a computerised random number generator. Treatments were administered by racetrack veterinarians. Following a minimum washout period of 2 weeks, horses were randomly assigned to another dosing group until all horses received all three dosing regimens. A 2-week washout period was observed to ensure that there were no residual diuretic nor haemodynamic effects, and to minimise the impact of the previous BAL on BAL cytology; it was also done to maximise clearance of RBC resulting from an EIPH episode that may have occurred during the previous simulated race, as recommended by Langsetmo *et al.* [15] based on the results of Meyer *et al.* [16].

Simulated race

Simulated races were run in pairs over a distance of 5 furlongs to simulate competitive racing on either a synthetic or dirt surface. Each horse was timed individually to determine actual speed.

Drug concentration determination

Blood samples for determination of drug concentration were collected immediately prior to the 4- or 24-h furosemide administration and following the simulated race. Samples were collected by direct venipuncture into serum separator blood tubes. Samples were centrifuged at 3000× *g* and the serum was immediately transferred into storage cryovials and stored at −20°C until analysed.

Furosemide concentrations in blood were determined using Liquid Chromatography-tandem Mass Spectrometry as described previously [17].

Physiologic measurements

Heart rate measurements: Horses wore a strap with two ECG electrodes[a] and riders wore an equine heart rate monitor watch (Equine RC3 GPS)[a] that recorded heart rates during the simulated races.

Endoscopic examination of airways: Approximately 1-h after each run, horses were sedated with a combination of xylazine (60–100 mg i.v.; Anased®)[b], detomidine (6–7 mg i.v.; Dormosedan®)[c] and butorphanol (7 mg i.v.; Tobugesic®)[c] and their airways were examined with a 3-m videoendoscope[d] for evidence of EIPH. Horses were assigned an EIPH grade by an investigator with extensive experience performing endoscopic exams and blinded to the treatment, according to previously described criteria [6] (Table 1). The endoscopic exam was recorded and three experienced racetrack veterinarians, blinded to the identity of the horse and the treatment received, independently assigned an EIPH grade score to each horse-run at a later date using the same criteria as described for the initial examination (Table 1).

TABLE 1: EIPH scoring system

Grade	Description
0	No blood detected in the pharynx, larynx, trachea or mainstream bronchi.
1	Presence of 1 or more flecks of blood or 2 or fewer short (less than one quarter the length of the trachea), narrow (<10% of the tracheal surface area) streams of blood in the trachea or mainstream bronchi visible from the tracheal bifurcation.
2	One long stream of blood (greater than half the length of the trachea) or more than 2 short streams of blood occupying less than a third of the tracheal circumference.
3	Multiple, distinct streams of blood covering more than a third of the tracheal circumference, with no blood pooling at the thoracic inlet.
4	Multiple coalescing streams of blood covering more than 90% of the tracheal surface with blood pooling at the thoracic inlet.

Bronchoalveolar lavage: Immediately following endoscopic examination of the airways, a 2.4-m long, 11-mm OD bronchoalveolar lavage (BAL) tube[e] was passed blindly via the right nostril. Prior to passing the BAL tube, the nostrils were cleaned with gauze and water and 30 mL of lidocaine 2%[f] was administered into each nostril using a Foley catheter. The BAL tube was advanced into the lung until wedged in a bronchus in the dorsocaudal region. Lidocaine (15 mL diluted in 15 mL Phosphate Buffered Saline [PBS]) was introduced into the BAL tube as the tube was advanced into the lungs to suppress coughing and alleviate discomfort to the horse. Ten mL (volume of the BAL tube) of PBS (pH 7.4 and 300 mOsm) was infused into the tube and the BAL tube cuff inflated with air. Five 60-mL aliquots of PBS were infused sequentially into the bronchus. After a brief mixing time (approximately two breaths), 10-mL of PBS was aspirated from the BAL tube and discarded. The reminder of the infused fluid was aspirated slowly and the volume collected was recorded. With the BAL tube still in place, the endoscope was passed through the left nostril to determine whether the BAL tube was lodged in the right or left lung. With the endoscope still in place, the BAL tube cuff was deflated and the tube was retracted and repositioned in the opposite lung. Once the BAL tube was confirmed to be in the opposite lung, the endoscope was withdrawn, dilute lidocaine was infused as the BAL tube was advanced until it wedged, and the BAL procedure was repeated.

The samples collected from the left and right lungs were processed and analysed separately. The white, foamy surfactant-rich fraction was removed from each syringe and the volume of liquid in each was recorded before all aliquots from the same lung were combined in a glass flask containing heparin. The recovered fluid was centrifuged at 500× *g* for 15 min. The pellet was reconstituted with PBS using a 1:40 dilution and an aliquot submitted for analysis. The number of RBC per mL of recovered fluid was determined by the Clinical Pathology Laboratory of the William R. Pritchard Veterinary Medical Teaching Hospital of the University of California, Davis, using their standard protocols.

Determination of haemoglobin, lactate and electrolyte concentrations: Samples of venous blood were collected for determination of total haemoglobin, lactate and K^+, Na^+, Ca^{2+}, Cl^- and HCO_3^- concentrations immediately prior to and following each simulated race. Samples were collected into PICO blood glass safety syringes[g] which were subsequently capped to prevent introduction of air into the syringe and placed on ice until analysis (4–6 h). Analysis was conducted using an ABL90 FLEX analyser[h]. Values are reported as mean ± s.d. for each dose group.

TABLE 2: Serum furosemide concentrations following intravenous administration of 250 mg of furosemide to 15 Thoroughbred racehorses either 4- or 24-h prior to maximal exercise. Samples were collected prior (7-min to 1-h and 26-min, and 5-min to 1-h and 40-min for the 4- and 24-h groups, respectively) and following (9- to 32-min and 9- to 34-min for 4- and 24-h groups, respectively)

	4-h furosemide		24-h furosemide	
Time	Average ± s.d. (ng/mL)	Median (Range) (ng/mL)	Average ± s.d. (ng/mL)	Median (Range) (ng/mL)
Pre-run	17.0 ± 2.7	16.9 (11.3–21.7)	0.18 ± 0.05	0.17 (0.10–0.27)
Post-run	16.7 ± 3.4	16.7 (10.3–25.5)	0.20 ± 0.07	0.18 (0.10–0.33)

Data analysis

Assessment of endoscopic EIPH scores comparing the three treatment groups was initially performed using an exact Friedman test, followed by pairwise exact Wilcoxon signed-rank test to compare individual groups to each other. Assessment of endoscopic EIPH scores between evaluators within treatment groups was performed using an exact Friedman test. Following creation of models for assessment of RBC count, haemoglobin, lactate and electrolyte concentrations, standardised residuals were calculated and evaluated for meaningful departures from normality by creating normal probability plots. Transformations of dependent variables (e.g. natural logarithm) were used when appropriate to normalise the residual distribution. In addition, the residuals were plotted against the treatment groups to evaluate homoscedasticity. Model assumptions were fulfilled in the final models presented. Mixed effects linear regression analysis was used to test for differences in log transformed RBC counts with horse treated as a random effect and treatment, lung side and run time as fixed effects. Mixed effects linear regression analysis was also used to test for differences in haemoglobin, lactate and electrolyte concentrations between each treatment group; horse was treated as a random effect and treatment, time (pre- and post-run), and their interaction with treatment were also included in the model as fixed effects. Significance was set at $P \leq 0.05$ for all tests.

Results

Forty-two of the 43 simulated runs were run in pairs. Twenty-one of 43 runs were run on a synthetic surface[i] and 22/43 runs were run on dirt surfaces[j,k]. Horses completed the 5-furlong run in times ranging from 59.33 to 65:00 s (62.53 ± 1.28 [mean ± s.d.]). The maximum recorded heart rates during the simulated races ranged from 201 to 225 bpm. Serum samples for determination of furosemide concentrations were collected both pre- and post-run. Sample collection times for the pre-run samples ranged from 7 min to 1-h and 26 min and 5-min to 1-h and 40 min prior to the run for the 4 and 24-h furosemide groups, respectively. Post-run sample collection times ranged from 9 to 32 min and 9 to 34 min for the 4- and 24-h furosemide groups, respectively. Furosemide concentrations are listed in Table 2. Thirteen of the 15 horses completed all three simulated races. The remaining two horses completed two (4- and 24-h furosemide administrations) of the three simulated races. Both horses missed one simulated race due to lameness, one prior to the second run and the second horse prior to the final run.

Individual EIPH scores for each horse, following each treatment, are in Table 3. Based on evaluation by the investigator who assigned an EIPH score in real time, 93% of the horses had post-race EIPH scores of 0 when furosemide was administered 4-h prior to the simulated race, 60% had a score of 0 at 24-h post-furosemide administration; 69% had a score of 0 post-saline administration. There was a difference in EIPH scores between the 4- and 24-h ($P = 0.03$) furosemide administrations, but no difference between the saline group and either furosemide treatment group. Comparison of EIPH scores assigned by all evaluators is in Table 4. EIPH scores between evaluators were significantly different in the 4-h furosemide group ($P = 0.01$). With blind passage of the BAL tube via the right nostril, the tube fell first into the right lung 30/43 times and first into the left lung 13/43 times. It was not possible to collect a BAL sample from the right lung from one horse in the saline group and from one horse in the 4-h furosemide group. The average recoveries of BAL fluid from the right lung were 49.6, 42.9 and 48.6% for saline, 4-h furosemide and 24-h furosemide groups, respectively, and 56.6, 53.2 and 59.6% from the left lung for saline, 4-h furosemide and 24-h furosemide groups, respectively. Individual horse RBC counts from BAL fluid collected from the right and left lungs, along with run times, are listed by treatment in Supplementary Item 1. The average RBC counts for each horse, as well as the order of the treatments in most effectively reducing the number of RBC, are in Supplementary Item 2. The average RBC count for each dose group is in Fig 1. There was no difference in RBC count between the right and left lungs within a treatment group. There was a difference in RBC count between the saline and 4-h furosemide treatment groups ($P = 0.01$), but no difference between the saline and 24-h furosemide treatment groups ($P = 0.2$) nor between the 4- and 24-h treatment groups ($P = 0.6$).

TABLE 3: EIPH scores following intravenous administration of 250 mg of furosemide or 5 mL of 0.9% NaCl to 15 Thoroughbred racehorses either 4- or 24-h prior to maximal exercise. Endoscopy was performed approximately 1 h post-run by an investigator blinded to treatment

Horse number	0.9% Saline (n = 13)	4-h Furosemide (n = 15)	24-h Furosemide (n = 15)
1	0	0	0
2	1	0	1
3	0	0	0
4	0	0	0
5	—	0	1
6	0	0	1
7	0	0	0
8	—	0	0
9	1	0	1
10	0	0	0
11	0	0	0
12	1	0	0
13	0	0	0
14	2	1	3
15	0	0	2
Median (range)	0 (0–2)	0 (0–1)[b]	0 (0–3)[a]

[a]Significantly different from 4-h furosemide group.
[b]Significantly different from 24-h furosemide group.

Blood samples for determination of total haemoglobin, lactate concentration and electrolyte concentrations pre- and post-run were collected at the times listed above for determination of furosemide concentrations. Sample collection times for the saline group ranged from 13 to 43 min and 14 to 36 min for pre- and post-run samples, respectively; all values are in Supplementary Item 1. Significant differences were noted between treatment groups when controlling for time (pre- and post-run) for potassium (4-h vs. 24-h furosemide, $P = 0.03$), sodium (saline vs. 24-h furosemide, $P = 0.01$), calcium (saline vs. 24-h furosemide, $P = 0.03$; 4-h vs. 24- h furosemide, $P = 0.04$) and chloride (saline vs. 4-h furosemide, $P = 0.05$; 4-h vs. 24-h furosemide, $P = 0.002$). There was a significant increase in haemoglobin ($P<0.01$), lactate ($P<0.01$), potassium ($P = 0.003$) and sodium ($P<0.01$) concentrations in post-collection time compared with precollection time after controlling for treatment group. There was a significant decrease in calcium ($P = 0.01$) and bicarbonate ($P<0.01$)

TABLE 4: Comparison of EIPH scores as assigned by four evaluators following i.v. administration of 250 mg of furosemide or 5 mL of 0.9% NaCl to 15 Thoroughbred racehorses either 4- or 24-h prior to maximal exercise. Endoscopy was performed approximately 1-h post-run. Evaluator #1 assigned scores in real time

	Saline (n = 13)				4-h Furosemide (n = 15)				24-h Furosemide (n = 15)			
	Evaluator											
Horse No.	#1	#2	#3	#4	#1	#2	#3	#4	#1	#2	#3	#4
1	0	0	0	0	0	0	0	0	0	0	0	0
2	1	1	1	1	0	0	0	0	1	1	1	1
3	0	1	1	1	0	0	0	0	0	0	0	0
4	0	0	1	0	0	0		0	0	0	1	1
5	—	—	—	—	0	0	0	0	1	1	1	1
6	0	0	0	0	0	0	1	0	1	1	1	1
7	0	0	0	0	0	1	1	1	0	0	0	0
8	—	—	—	—	0	0	0	0	0	0	0	0
9	1	1	2	2	0	0	0	0	1	1	2	1
10	0	0	0	0	0	0	1	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	1	0
12	1	1	1	1	0	0	0	0	0	0	0	0
13	0	0	1	0	0	0	0	0	0	1	1	1
14	2	2	2	2	1	1	2	1	3	3	3	2
15	0	0	0	1	0	0	1	0	2	2	2	1
Median (range)	0 (0–2)	0 (0–2)	1 (0–2)	0 (0–2)	0 (0–1)[a]	0 (0–1)[a]	0 (0–2)[a]	0 (0–1)[a]	0 (0–3)	0 (0–3)	1 (0–3)	1 (0–2)

[a]Scores were significantly different between evaluators.

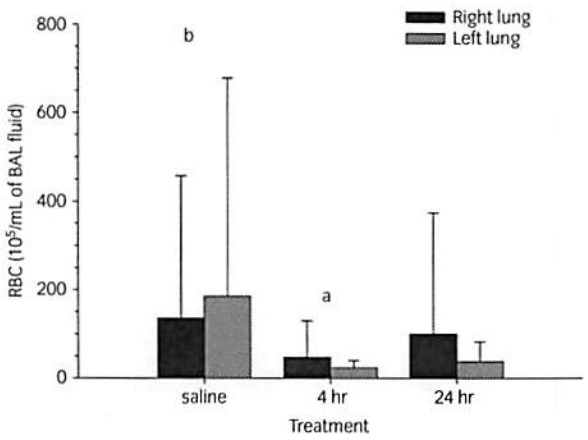

Fig 1: Red blood cell counts (RBC) in bronchoalveolar lavage fluid collected 1-h post-maximal exercise from 15 Thoroughbred racehorses following administration of 0.9% saline i.v. 4-h prior to exercise; 250 mg of furosemide i.v. 4-h prior to exercise; or 250 mg of furosemide i.v. 24-h prior to exercise. The RBC count was different between 4-h furosemide administration and saline (a, b; P = 0.01); not different between 24-h furosemide administration and saline (P = 0.1); and not different between 4- and 24-h furosemide administration (P = 0.6).

concentrations in post-collection time compared with precollection time after controlling for treatment group.

Discussion

Previous studies have described the effects of furosemide on EIPH in both field trials and with horses actively in race training [4,7] as well as with horses running on a high-speed treadmill [14]. The current study expands upon these previous studies by assessing the effects of furosemide in actively racing Thoroughbred horses, utilising a combination of endoscopic examination of the airways and assessment of RBC counts in BAL fluid. Furthermore, we sought to assess whether furosemide administered 24-h prior to racing would be as effective in reducing the severity of EIPH as administration at 4-h prior to racing based on both diagnostic procedures.

In the current study, horses were enrolled without any prior knowledge by the investigators as to whether they had previously been diagnosed with EIPH. There was no difference between EIPH scores in horses receiving furosemide either 4- or 24-h prior to the simulated race and those administered saline. This is in contrast to a previous report in which furosemide decreased EIPH scores relative to saline in control horses [4,7]. One possible explanation for the disparate research findings may be that the number of horses evaluated in the study reported by Pascoe and colleagues [4] (62 horses) and Hinchcliff and colleagues [7] (152 horses) were much greater than in the current study. It is conceivable that had a larger number of horses been enrolled in the current study, that the differences between the saline and furosemide treatment groups may have been significant. The EIPH status of the horses was unknown at the time of enrolment, whereas in the Pascoe *et al.* [4] study, a large percentage of the horses studied were known to have EIPH prior to treatment. The studies were also conducted under different conditions: the present study under breezing, and the larger study under racing conditions; these conditions could have modified the effect of furosemide relative to the placebo. Finally, the present study relied on a crossover design to ensure that all horses received each treatment, unlike the larger study that was group randomised. Horses enrolled in the current study generally had low EIPH scores (0 and 1), regardless of treatment, compared with previous track studies [4,7]. Differences in EIPH scores may have been noted between the furosemide and saline treatment groups had more horses with a known history of EIPH been studied or if horses with clinically problematic EIPH had been selected. Furosemide appears to be more effective in reducing higher EIPH scores [7]. It should also be noted that only 13 of the 15 horses were treated with saline prior to the run, whereas both furosemide treatment groups had 15 horses. The lower sample size in the saline treated group could have reduced the ability to detect differences between the saline and furosemide treatment groups. Another possible, but less likely, explanation for the disagreement between the two studies is that furosemide was administered 1-h prior to work in the study conducted by Pascoe and colleagues [4] compared with 4- or 24-h prior to a high-intensity run in the current study. While it is possible that the shorter time of furosemide administration before working decreased the intensity of the EIPH-associated haemorrhage in the Pascoe *et al.* study [4], other reports suggest that there is a lag time of several hours before pulmonary

haemodynamics are affected [13]. Despite the limitations detailed above, EIPH scores in the current study were lower when horses received furosemide 4-h prior to a run compared with administration 24-h prerun, suggesting that administration at 4-h may be more effective in decreasing the amount of endoscopically visible haemorrhage compared with 24-h.

Although endoscopy is commonly used in racetrack practice to diagnose EIPH, several studies have demonstrated that this is not the most sensitive method for diagnosis as it does not include assessment of the terminal airways and alveolar spaces [16,18,19]. Furthermore, horses that are ultimately diagnosed with EIPH using more sensitive methods do not necessarily have signs of haemorrhage on endoscopic examination [16,20]. Bronchoalveolar lavage has been shown to be a much more sensitive means by which to diagnose and assess the severity of EIPH [20]. Endoscopic EIPH scores did not appear to correlate with the results of RBC counts from BAL in this study. Based on the presence of RBC in the BAL fluid, all 15 horses experienced some degree of EIPH during all runs and with all three treatment protocols (a total of 43 runs). Only 11 (26%) of these runs were associated with endoscopically visible haemorrhage (grade 1 or higher), whereas the remaining 74% showed no visible haemorrhage (grade 0). It is important to note that although all horses experienced some degree of EIPH upon analysis of BAL fluid, the clinical significance and effect on performance remains to be determined.

The BAL tube was passed a total of 43 times in the current study. In each horse, the tube was initially passed blindly via the right nostril and in 30 (70%) of those cases the tube fell first into the right lung and in 13 (30%) cases it went first into the left lung. This is consistent with previous reports whereby in the majority of cases of blind passage resulted in the BAL tube naturally falling into the right lung [21–23]. It has been proposed that the propensity for the BAL tube to naturally fall into the right lung upon blind passage may be related to the straighter disposition of the right mainstem bronchus compared with the left [24]. Also attributed to the anatomical differences in the right and left main stem bronchus are differences in neutrophil and haemosiderophage percentages and haemosiderophage/macrophage (H/M) ratios [24] as well as a higher incidence of aspiration bronchopneumonia in the right vs. the left lung [25]. In contrast, reports describing RBC counts in BAL fluid collected from horses with EIPH reported no difference in RBC numbers between the right and left lungs [16]. This is similar to findings in the current study whereby there was no difference in mean RBC counts between the right and left lungs within treatment groups; however, substantial differences between the right and left lung were observed in individual horses.

One of the primary objectives of the current study was to compare the efficacy of furosemide in reducing EIPH as measured by RBC counts when administered 4- vs. 24-h prior to maximal exercise. The RBC counts were lower when furosemide was administered 4-h prior to high-intensity exercise compared with horses receiving saline, whereas there was no difference in RBC counts between saline and 24-h furosemide administration or between 4- and 24-h furosemide administration. Although the average RBC count was not different between 4 and 24-h furosemide administration, the majority of horses had the lowest average RBC count following 4-h furosemide administration, suggesting a trend of reduced bleeding with 4-h vs. 24-h furosemide administration. This suggestion is further supported by the comparisons between 4-h vs. saline (difference) and 24-h vs. saline (no difference).

One notable limitation in the current study is the sample size. Inclusion of additional horses may have yielded a more definitive conclusion regarding the efficacy of administration of furosemide at 4- vs. 24-h prior to high-intensity exercise. Although inclusion of horses in the current study was not made based on EIPH status, the severity of EIPH in the horses in this study appears to be lower than in previous studies. Additionally, horses enrolled in the current study had a range of athletic abilities, with running times ranging from 59.33 to 65.00 s (mean of 62.53 s) for 5 furlongs. While this range of athletic abilities is likely representative of the population of Thoroughbred horses racing in North America, it is possible that inclusion of a greater proportion of faster or slower horses may have yielded a more definitive answer. Previous studies have concluded that furosemide appears to be more effective in horses that run with faster vs. slower times [26].

This study describes in racing Thoroughbred horses the effects of furosemide administered 4- and 24-h prior to maximal exertion on endoscopic EIPH scores and RBC counts in BAL fluid. Based on EIPH scores, findings in the current study support previous findings of the efficacy of furosemide administration in reducing the severity of EIPH in horses but do not support anecdotal reports of equivalent efficacy of furosemide in attenuating bleeding when administered 4- and 24-h prerace. The lack of a difference in RBC counts between horses receiving saline and those receiving furosemide 24-h prerace, coupled with a difference in RBC counts between the saline and 4-h furosemide groups, suggests that 24-h administration is not as efficacious as 4-h administration in attenuating the haemorrhage associated with EIPH. However, the lack of a difference in RBC counts between the 4- and 24-h furosemide groups confounds this interpretation. While all horses showed cytological evidence of bleeding with all three treatments and none of the treatments prevented EIPH, 4-h furosemide administration appeared to most effective in reducing severity.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

The study was approved by the Institutional Animal Care and Use Committee and the Clinical Trials Review Committee of the University of California, Davis. Owner consent was obtained prior to enrolment in the study.

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Authorship

H.K. Knych and W.D. Wilson contributed to study design, study execution, data analysis and interpretation, and preparation of the manuscript. A. Vale contributed to study execution. P.H. Kass contributed to data analysis and interpretation. R.M. Arthur and J.H. Jones contributed to study design, study execution, and data analysis and interpretation. All authors gave their final approval of the manuscript.

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[d]Portoscope, Bradenton, Florida, USA.
[e]Mila International, Inc, Florence, Kentucky, USA.
[f]VetOne, Boise, Idaho, USA.
[g]Radiometer, Brea, California, USA.
[h]Radiometer Medical, Bronshoi, Denmark.
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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplementary Item 1: Red blood cell counts in bronchoalveolar lavage fluid.

Supplementary Item 2: Mean (right and left lungs) red blood cell counts (RBC) in bronchoalveolar lavage fluid.

Supplementary Item 3: Red blood cell counts (RBC) in bronchoalveolar lavage fluid.

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ORIGINAL ARTICLE

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Pharmacokinetics of furosemide administered 4 and 24 hours prior to high-speed exercise in horses

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Furosemide is a diuretic agent used commonly in racehorses to attenuate the bleeding associated with exercise-induced pulmonary hemorrhage (EIPH). The current study describes serum and urine concentrations and the pharmacokinetics of furosemide following administration at 4 and 24 hrs prior to maximal exercise. Eight exercised adult Thoroughbred horses received a single IV administration of 250 mg of furosemide at 4 and 24 hrs prior to maximal exercise on a high-speed treadmill. Blood and urine samples were collected at time 0 and at various times for up to 72 hrs and furosemide concentrations determined using liquid chromatography–tandem mass spectrometry. Serum furosemide concentrations remained above the LOQ (0.05 ng/ml) for 36 hrs in 3/8 and 1/8 horses in the 4- and 24-hrs groups, respectively. Serum concentration data were best fit by a two-compartment model. There was not a significant difference in the volume of distribution at steady-state (0.594 ± 0.178 [4 hrs] and 0.648 ± 0.147 [24 hrs] L/kg) or systemic clearance (0.541 ± 0.094 [4 hrs] and 0.617 ± 0.114 [24 hrs] L/hrs/kg) between horses that were exercised at 4- and 24 hrs postdrug administration. The mean ± *SD* elimination half-life was 3.12 ± 0.387 and 3.23 ± 0.407 hrs following administration at 4 and 24 hrs prior to exercise, respectively.

1 | INTRODUCTION

Furosemide is a diuretic agent used commonly in racehorses to attenuate the bleeding associated with exercise-induced pulmonary hemorrhage (EIPH). Due to the high prevalence of EIPH in racehorses, administration of furosemide is permitted up to 4 hrs prior to race, making it a permitted race day medication in North America. Recently, it has been suggested that furosemide may be equally effective in reducing the severity of EIPH when administered 24 hrs prior to a race as when administered 4 hrs before a race (Warwick Bayly, personal communications).

Although blood concentrations of furosemide have been described previously, drug concentrations have only been reported for 6–8 hrs postadministration (Chay et al., 1983; Dirikolu et al., 2003). Dirikolu et al. (2003) collected samples until 24 hrs postfurosemide administration; however, concentrations were only reported up to

6 hrs postadministration. Furosemide concentrations at 6 hrs postadministration were below the limit of quantitation (3.9 ng/ml) in 3/10 horses and ranged from 5 to 9.5 ng/ml in the remaining seven horses (Dirikolu et al., 2003). If furosemide were to be demonstrated to be as effective at 24 hrs postadministration in reducing the severity of EIPH and the prerace administration time were moved to 24 hrs, regulatory laboratories would need to increase the sensitivity of their analytical methods to accommodate the rule change. Therefore, the objective of the current study was to develop a highly sensitive assay that could be used to quantify serum furosemide concentrations for a minimum of 24 hrs postdrug administration. Additionally, we sought to describe the pharmacokinetics of furosemide when horses were exercised at 4 and 24 hrs postdrug administration.

2 | MATERIALS AND METHODS

2.1 | Horses

Eight healthy, University-owned and exercised Thoroughbred horses, three mares and five geldings, (age 3–6 yr; weight 502 ± 36.1 kg [4 hrs]; 495 ± 46.5 [24 hrs] [mean ± *SD*]), were studied. No medications were administered for a minimum of four weeks prior to commencement of the study. Before beginning the study, horses were determined to be healthy by physical examination, complete blood count and a serum biochemistry panel. Blood analyses were performed by the Clinical Pathology Laboratory of the William R. Pritchard Veterinary Medical Teaching Hospital of the University of California, Davis, using standard protocols. The study was conducted with approval of the Institutional Animal Care and Use Committee of the University of California, Davis.

All horses used in the study are part of the regularly exercised research herd at the University of California, Davis, and are accustomed to running on a high-speed treadmill (Mustang, Graber AG, Switzerland). For the first 5 weeks prior to commencement of the study, horses were exercised for 3 days each week on the high-speed treadmill at 0% grade according to the following protocol: walk (2 m/s) for 5 min, trot (4 m/s) for 3 min, canter (7 m/s) for 2 min, gallop at 10 m/s and 14–15 m/s for 1 min each, followed by a cool-down. For the final 3 weeks prior to dosing, the same regimen was followed with the treadmill inclined to a 4% grade. On days that horses were not exercised on the treadmill (4 days per week), they were exercised on an Equineciser (Centaur Horse Walkers Inc, Mira Loma, CA, USA). Three of those days consisted of a 5-min walk, 30-min trot followed by a 5-min walk. The fourth day consisted of a 20-min walk.

2.2 | Study design, instrumentation and drug administration

Prior to drug administration, a 14-gauge catheter was placed in one external jugular vein for sample collection. Each horse was weighed immediately prior to drug administration. This study was conducted in a randomized, balanced two-way crossover design. Randomization was performed by an investigator who was not involved in drug administration. All horses received both treatments, and the order of administrations to each horse was determined using a random number generator. Horses were randomly assigned to receive 250 mg (5 ml) of furosemide (Salix® 50 mg/ml, Merck Animal Health, Elkhorn, NE) IV 4 hrs prior to exercise or 250 mg (5 ml) furosemide IV 24 hrs prior to exercise. All drugs were administered directly into the jugular vein. Water was withheld starting immediately after dosing for horses in the 4-hrs furosemide group. Horses receiving furosemide 24 hrs prior to the treadmill exercise received 2.5 L of water every 4 hrs until 4 hrs prior to exercise, at which time water was withheld. All horses had free access to water within one hour of completion of the treadmill run. Horses were exercised at 4 or 24 hrs postdrug administration on a high-speed treadmill according to the following protocol. Horses warmed up at a walk (2 m/s) and trot (4 m/s) on a 0% incline. Following the warm-up period, the treadmill was elevated to a 4% grade and the speed increased to 7 m/s for 1 min, after which the treadmill speed was increased to induce the horse to gallop at a speed determined during the training runs to elicit maximal heart rate that the horse could maintain for 1 min. Following a minimal washout period of 2 weeks, horses were assigned to the other dosing group until all horses had received both dosing regimens.

2.3 | Sample collection

2.3.1 | Blood

Blood samples for determination of drug concentrations were collected at time 0 (prior to drug administration) and at 5, 10, 15, 30, and 45 mins after, and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48 and 72 hrs postfurosemide administration. Samples were collected via a jugular vein intravenous catheter. Catheters were removed following collection of the 24-hrs sample, and the remaining samples were collected by direct venipuncture. Blood samples were collected into serum separator blood tubes and centrifuged at 3000 × *g*. Serum was immediately transferred into storage cryovials and stored at −20°C until analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS).

2.3.2 | Urine

Urine samples were collected from all horses via free catch for measurement of furosemide concentrations. Samples were collected on Day 0 (prior to drug administration), at 4 hrs and 24 hrs postdrug administration and on days two and three postfurosemide administration. For horses in the 4- and 24-hrs administration groups, samples were collected immediately after horses finished their treadmill run. Specific gravity and total protein were measured using an optical refractometer. Samples were stored at −20°C until analysis by LC-MS/MS.

2.4 | Drug concentration determination

2.4.1 | Serum sample analysis

Furosemide working solutions were prepared by dilution of 1 mg/mL stock solutions (Cerilliant, Round Rock, TX) with methanol to concentrations of 0.01, 0.1, 1, 10 and 100 ng/μl. Serum calibrators were prepared by dilution of the working standard solutions with drug-free equine serum to concentrations ranging from 0.05 to 4000 ng/ml. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality control samples (serum fortified with analyte at three different concentrations within the standard curve) were included with each sample set as an additional check of accuracy.

Prior to analysis, 1 ml of serum was diluted with 100 μl of water containing d5-furosemide (Toronto Research Chemicals, Toronto, ON) internal standard at 5 ng/ml. Two-hundred and fifty microliters of 0.2 N HCl was added to adjust the sample pH to 5, and the samples were vortexed briefly to mix. Five milliliters of methyl tert-butyl ether:methylene chloride (60:40, v:v) was added to each serum sample, and the samples were mixed by rotation for 20 min at 40 rpm. After rotation, samples were centrifuged at 2260 g for 5 min at 4°C. The top organic layer was transferred to a 12 × 75 mm glass tube, and samples were dried under nitrogen and dissolved in 120 μl of 5% acetonitrile in water, both with 0.2% formic acid. The injection volume was 40 μl into the LC-MS/MS system.

The concentration of furosemide was measured in serum by LC-MS/MS using negative heated electrospray ionization. Quantitative analysis of serum was performed on a TSQ Vantage triple-quadrupole mass spectrometer (Thermo Scientific, San Jose, CA) coupled with a turbulent flow chromatography system (TFC TLX2 Thermo Scientific, San Jose, CA) having LC-10ADvp liquid chromatography systems (Shimadzu, Kyoto, Japan) and operated in laminar flow mode. The spray voltage was 3000V, and the sheath and auxiliary gas were 45 and 30, respectively (arbitrary units). Product masses and collision energies of each analyte were optimized by infusing the analytes into the mass spectrometer. Chromatography employed an ACE 3 C18 10 cm × 2.1 mm 3 μm column (Mac-Mod Analytical, Chadds Ford, PA) and a linear gradient of acetonitrile (ACN) in water with a constant 0.2% formic acid at a flow rate of 0.35 ml/min. The initial ACN concentration was held at 10% for 0.5 min, ramped to 90% over 5.5 min, held at that concentration for 0.17 min, before re-equilibrating for 4 min at initial conditions.

Detection and quantification were conducted using selective reaction monitoring of initial precursor ion for furosemide (mass to charge ratio (*m/z*) 328.9) and d5-furosemide ((*m/z*) 333.9). The response for the product ions for furosemide (*m/z* 121.1, 204.8, 285.9) and d5-furosemide (*m/z* 205.8) was plotted, and peaks at the proper retention times were integrated using Quanbrowser software (Thermo Scientific, San Jose, CA). Quanbrowser software was used to generate calibration curves and quantify furosemide in all samples by linear regression. The method validation process met with Association of Racing Commission (AORC) MS guidelines. A weighting factor of 1/X was used for all calibration curves.

2.4.2 | Urine sample analysis

Furosemide working solutions were prepared as described above. Urine calibrators were prepared by dilution of the working standard solutions with drug-free equine urine to concentrations ranging from 1 to 6000 ng/ml. Calibration curves and negative control samples were prepared freshly for each quantitative assay. In addition, quality control samples (urine fortified with analyte at three different concentrations within the standard curve) were included with each sample set as an additional check of accuracy.

Prior to analysis, 1 ml of urine was diluted with 200 μl of water containing d5-furosemide internal standard at 50 ng/ml and 0.4 ml of β-glucuronidase enzyme, (Sigma Aldrich, St. Louis, MO) at 10,000 Units/ml at pH 5 and 1.6 M acetate buffer. The samples were vortexed briefly to mix and the pH of the samples was adjusted to 5 ± 0.5 with 2 N NaOH or 2 N HCl, as necessary. Samples were heated in a sonicating Branson water bath (Danbury, CT) at 65°C for 2 hrs with 99 min of sonication. After cooling to room temperature, 1.4 ml of 0.6 M pH 6.5 phosphate buffer was added to the samples and the samples were vortexed briefly to mix them and were then subjected to solid phase extraction using Cerex polycrom Clin II 3 cc 35-mg columns (Cera, Inc. Baldwin Park, CA). Samples were loaded onto the columns over a minimum of at least 2 min, washed consecutively with 3 ml of water, 2 ml of 1.0 M acetic acid, and 3 ml of hexane prior to elution with 3 ml of ethyl acetate:hexane (1:1 v:v). Samples were dried under nitrogen at 45°C and reconstituted in 160 μl of 5% ACN in water, both with 0.2% formic acid. The injection volume was 40 μl into the LC/MS system.

Detection and quantification were the same as described above except the quantitative ion used for quantitation for furosemide was (*m/z* 206) and for d5-furosemide was (*m/z* 205.8, 289.9).

2.5 | Pharmacokinetic analysis

Compartmental analysis was used for determination of pharmacokinetic parameters for intravenously administered furosemide using commercially available software (Phoenix WinNonlin 6.2 (Certara, St. Louis, MO). Goodness of fit and the appropriate weighting factor were selected based on visual analysis of observed versus predicted concentration graphs and residual plots as well as coefficient of variation, Akaike information criterion (AIC; Yamaoka, Nakagawa, & Uno, 1978) and Schwarz's Bayesian criteria (SBC; Schwarz, 1978).

2.6 | Statistical analysis

Mixed-effects linear regression, with horse as the random effect, was used to evaluate the joint effects of time and treatment time on the natural log (ln) concentration of furosemide. An initial model with a time-by-treatment interactions was fit, and a global Wald test was used to test for the overall improvement of model fit by inclusion of the interaction terms. If the fit of the model with interactions was not significantly better than a main-effects-only model, then the latter was fit. Mixed-effects analysis of variance was used to compare the effects of paired treatments within horses (4 vs 24 hrs) on

pharmacokinetic parameters; results are presented as 95% confidence interval of the difference and *p*-values from testing the null hypothesis that treatment differences = 0.

3 | RESULTS

The coefficients of determination (R^2) for the furosemide serum and urine calibration curves were 0.99 or better. The intraday and interday precision and accuracy of the assay were determined by assaying quality control (QC) samples in replicates (n = 6) for furosemide at three concentrations within the curve including a QC level at three times the limit of quantitation (LOQ). Accuracy was reported as percent nominal concentration (% CV), and precision was reported as percent relative standard deviation (RSD) (Table 1). Accuracy and precision for both matrices were considered acceptable based on the Food and Drug Administration's guidelines for Bioanalytical Method Development. The LOQ was the lowest calibrator that could be measured with acceptable precision and accuracy. The limit of detection (LOD) was established based on the lowest calibrator with a 3:1 signal-to-noise ratio. The analytical method was optimized to provide an LOQ of 0.05 ng/ml and an LOD of approximately 0.025 ng/ml in serum and an LOQ of 1 ng/ml and LOD of 0.5 ng/ml in urine.

Mean furosemide serum concentration over time curves is depicted in Figure 1, and mean (±*SD*) serum furosemide concentrations is in Table 2. Serum concentrations for horses receiving furosemide 4 and 24 hrs prior to exercise were compared. There was no improvement of fit through the inclusion of a time-by-treatment interaction term (p = .603). After controlling for time, there was no association between treatment time and the ln furosemide concentration (p = .285). Serum furosemide concentrations remained above the LOQ (0.05 ng/ml) for 36 hrs in 3/8 in 4-hrs group and 1/8 in 24-hrs group (Figure 1; Table S1). Furosemide concentrations were no longer detectable at 48 hr postadministration. A two-compartment model ($C_p = Ae^{-\alpha t} + Be^{-\beta t}$) with a multiplicative weighting factor (C * (1 + Ceps)) gave the best fit to furosemide concentration data. The average (± *SD*) values for a number of pharmacokinetic parameters are listed in Table 2. The volume of distribution of the central compartment (V_1; 0.282 ± 0.210 [4 hrs] and 0.204 ± 0.036 [24 hrs] L/kg) and systemic clearance (Cl_1; 0.541 ± 0.094 [4 hrs] and 0.617 ± 0.114 [24 hrs] L/hrs/kg) were not different between horses that were exercised at 4- and those exercised at 24 hrs postdrug administration (Table 2). The volume of distribution at steady-state was also similar between horses that received furosemide at 4 hrs (0.594 ± 0.178 L/kg) and 24 hrs (0.648 ± 0.147 L/kg) prior to exercise (Table 2).

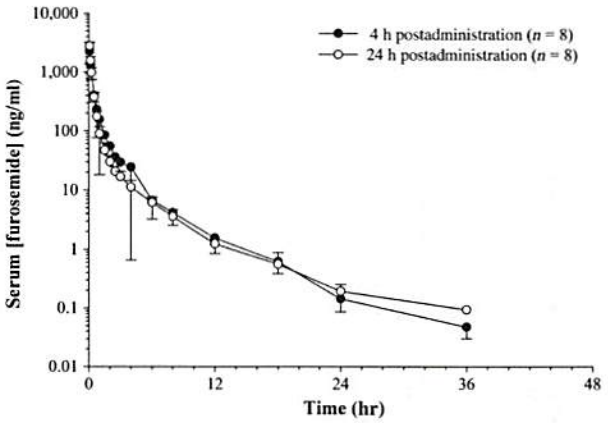

FIGURE 1 Mean ± *SD* serum furosemide concentrations following intravenous administration of 250 mg of furosemide to eight horses, 4 and 24 hrs prior to maximal exercise on a high-speed treadmill

The average (± *SD*) urine specific gravity, total protein and furosemide concentrations are reported in Table 3.

4 | DISCUSSION

In North America, furosemide is a permitted race day medication for the treatment EIPH. Anecdotal reports of the efficacy of furosemide in decreasing the severity of EIPH when administered 24 hrs prior to a race have led to discussions about changing the permitted administration time from 4 to 24 hrs prior to a race. However, currently furosemide concentrations have only been described for up to 8 hrs postadministration. The primary goal of the current study was to develop an analytical assay that would be sensitive enough to quantify furosemide concentrations for up to 24 hrs postadministration, should there be a change in current racing regulations to prohibit race day administration of furosemide. Previous studies have reported LOQs ranging from 3.9 to 15 ng/ml (Dirikolu et al., 2003; Dyke, Hinchcliff, Sams, McKeever, & Muir, 1996). In the study reported here, the LOQ was much lower (0.05 ng/ml), allowing for quantitation of furosemide concentrations until 24 hrs postadministration in all horses and up to 36 hrs in some horses. This assay would

TABLE 1 Accuracy and precision values for LC-MS/MS analysis of furosemide in equine serum and urine

Matrix	Concentration (ng/ml)	Intraday accuracy (% nominal concentration)	Intraday precision (% relative *SD*)	Interday accuracy (% nominal concentration)	Interday precision (% relative *SD*)
Serum	0.15	100	2.0	105	3.0
	25.0	101	3.0	99.0	4.0
	2000	100	6.0	102	5.0
Urine	1.5	96.0	6.0	97.0	9.0
	50.0	109	6.0	110	4.0
	4000	102	4.0	102	4.0

TABLE 2 Mean ± *SD* pharmacokinetic parameters, following a single intravenous of administration of 250 mg of Salix® to eight exercised Thoroughbred horses, 4 and 24 hrs prior to strenuous exercise

	4-hrs run	24-hrs run	
	Mean ± *SD*		[95% CI], *p*-value
A (ng/ml)	2541 ± 1531	2533 ± 508	[−1097, 567.1], $p = .533$
B (ng/ml)	27.2 ± 5.48	31.8 ± 5.88	[1.49, 11.3], $p = .011$
Alpha (1/h)	3.12 ± 1.42	3.67 ± 0.518	[−0.572, 0.931], $p = .640$
Beta (1/h)	0.205 ± 0.024	0.218 ± 0.024	[−0.004, 0.040], $p = .107$
$t_{1/2\alpha}$ (h)	0.339 ± 0.303	0.193 ± 0.032	[−0.170, 0.067], $p = .392$
$t_{1/2\beta}$ (h)	3.42 ± 0.387	3.23 ± 0.407	[−0.664, 0.076], $p = .119$
AUC_{last} (hrs*ng/ml)	959.6 ± 236.3	841.3 ± 132.5	[−266.8, 81.6], $p = .298$
Cl (L/(hrs/kg)	0.541 ± 0.094	0.617 ± 0.114	[−19.4, 172.1], $p = .118$
V_1 (L/kg)	0.282 ± 0.210	0.204 ± 0.036	[−215.2, 58.2], $p = .261$
V_{ss} (L/kg)	0.594 ± 0.178	0.648 ± 0.147	[−95.5, 203.9], $p = .478$

All pharmacokinetic parameters were generated using compartmental analysis. The 95% confidence interval of differences in means and *p*-values was generated from statistical analysis comparing 4- to 24-hrs values. A and B, intercepts at t = 0 for the model equation; alpha and beta, slopes for the modeled equation; V_1, volumes of the central compartment; V_{ss}, volume of distribution at steady-state (calculated as MRT * Cl); $t1_{/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; AUC_{last}, area under the curve until the last time point; Cl, total systemic clearance.

be suitable to adequately regulate the use of furosemide at 24 hrs postdose.

Serum furosemide concentrations in the current study were best fit by a two-compartment pharmacokinetic model, which is in agreement with the study reported by Roberts, Blake, and Tobin (1978) and Dirikolu et al. (2003). Chay et al. (1983) describe a triexponential equation as giving the best fit to drug concentration data. The reason for the discrepancy between the current study and that conducted by Chay et al. (1983) is not clear. A common phenomenon is the detection of additional compartments as assay sensitivity is improved and the ability to quantify lower and lower concentrations is achieved. In the current study, even with an increase in sensitivity, visual analysis of observed versus predicted concentration graphs indicated that the AIC and % CV values clearly demonstrated that the data were best fit by the simpler model.

The half-life ($t_{1/2\beta}$) in this study (3.42 ± 0.387 and 3.23 ± 0.407 hrs for the 4- and 24-hrs exercise groups, respectively) was prolonged compared to previous reports that ranged from 22.3 min to 1.83 hrs (Chay et al., 1983; Dirikolu et al., 2003; Roberts et al., 1978). The discrepancy between the studies is likely due to the greater sensitivity of the analytical assay developed for the current study that allowed for quantitation of drug concentrations for up to 24-36 hrs postdrug administration. Increased sensitivity, allowing for detection of lower concentrations, decreases the amount of extrapolation of the terminal portion of the plasma concentration curve, and therefore, increasing the accuracy of the estimate. The systemic clearance and volume of distribution at steady-state were similar to those reported previously (Cl: 0.385 – 0.642 L/hr/kg; V_{ss}: 0.164–0.363 L/kg) (Chay et al., 1983; Dirikolu et al., 2003; Dyke et al., 1996).

Exercise has been shown to have an effect on the pharmacokinetics of certain drugs (Dyke, Sams, & Hinchcliff, 1985, 1998; Powis & Snow, 1978; Ylitalo, 1991). Therefore, in the current study, we also sought to determine if serum concentrations and pharmacokinetic parameters were altered if horses were exercised at 4 hrs postadministration compared to 24 hrs. Dyke et al. (1996)evaluated the effects on the pharmacokinetics of furosemide of submaximal exercise consisting of a 60-min run on an inclined (6°) treadmill at a speed that would maintain a steady-state heart rate of 65% of maximal heart rate. The investigators concluded that prolonged submaximal exercise did

TABLE 3 Urine specific gravity, total protein and furosemide urine concentrations (mean ± *SD*) following IV administration of 250 mg of Salix® to eight exercised Thoroughbred horses, 4 and 24 hrs prior to strenuous exercise

	4-hrs run			24-hrs run		
Time (hrs)	Urine [furosemide] (ng/ml)	Specific Gravity	Total Protein	Urine [furosemide] (ng/ml)	Specific Gravity	Total Protein
0	ND	1.027 ± 0.005	3.81 ± 1.04	ND	1.025 ± 0.003	3.27 ± 0.60
4	6936 ± 6794	**1.021 ± 0.006**	**2.61 ± 0.99**	3034 ± 1770	1.021 ± 0.002	2.71 ± 0.39
24	67.7 ± 36.0	1.035 ± 0.003	5.49 ± 0.65	45.9 ± 16.7	**1.035 ± 0.003**	**5.42 ± 0.82**
48	4.01 ± 2.39	1.029 ± 0.004	4.09 ± 0.79	2.16 ± 0.45	1.028 ± 0.003	3.88 ± 0.73
72	ND	1.026 ± 0.004	3.63 ± 0.79	0.77 ± 0.26	1.029 ± 0.003	4.28 ± 1.26

Bold text indicates urine specific gravity and total protein values that correspond with immediate postexercise sample.

not influence plasma concentrations or the pharmacokinetics of furosemide (Dyke et al., 1996). However, as acute bouts of strenuous exercise, such as racing, induce different physiological responses, the effects of this type of exercise on furosemide pharmacokinetics may be different from that observed with submaximal exercise (Dyke et al., 1996). In the presently reported study, there were no statistically significant differences in serum concentrations, systemic clearance or the elimination $t_{1/2}$ between horses exercised at 4 and 24 hrs postdrug administration. Because horses were exercised after drug distribution was complete ($t_{1/2\alpha}$ of 0.339 and 0.193 hr for 4- and 24-hr exercise groups, respectively), if exercise affected distribution, it likely would not have been detected in the current study.

As a diuretic agent, administration of furosemide is associated with water loss, which can affect the volume of distribution. In the current study, in an attempt to mimic practices on the racetrack, water was withheld for 4 hrs prior to exercise. It is commonplace to restrict water intake so as not to replace that lost due to furosemide-induced diuresis. Replacement of the lost water could increase plasma volume, thereby increasing pulmonary vascular pressure. It is important to note, however, that diuresis coupled with water restriction could also potentially impact drug distribution. In the current study, horses receiving furosemide 4 hrs prior to exercise had water withheld immediately upon drug administration, while small amounts of maintenance water were provided until 4 hrs prior to exercise in the 24-hrs group. The steady-state volume of distribution and volume of the central compartment were not different between the groups. Furthermore, the volume of distribution in the current study was in agreement with that reported in other studies where water was not withheld following furosemide administration (Chay et al., 1983; Dirikolu et al., 2003), suggesting that the magnitude of water loss was not sufficient to affect drug distribution.

The current study describes serum concentrations and the pharmacokinetics of furosemide following administration at 4 and 24 hrs prior to exercise. Previously, furosemide concentrations have only been described for 8 hrs postdrug administration. In the study reported here, the development of a more sensitive analytical assay than has been previously reported allowed for quantitation of furosemide in serum samples for 24 hrs in all horses and 36 hrs in four horses (three in the 4-hrs and one in the 24-hrs groups) postdrug administration. It is important to note that in many racing jurisdictions, regulation of furosemide 4 hours prior to race is based on a combination of serum concentrations (>100 ng/ml) and urine specific gravity (<1.010). The results of this study suggest that this regulatory approach would no longer be applicable if a 24-hrs furosemide restriction was to be implemented as urine specific gravity does not appear to be a relevant marker 24 hrs postfurosemide administration. Additionally, serum concentrations and systemic clearance were not different between horses exercised at 4 and 24 hrs postfurosemide administration.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Lasix Study Backs Four-Hour Administration Time

A study that has some potential to reshape the timing of Salix administration ahead of racing determined that the current four-hour timeframe is more effective than administering 24 hours out in reducing the severity of exercise-induced pulmonary hemorrhage.

The study, led by Dr. Heather Knych, was one of two studies on Salix (furosemide, commonly referred to as Lasix) with results outlined at the American Association of Equine Practitioners convention in late November. The other study, led by Dr. Warwick Bayly, found some potential for a low dosage of Salix 24 hours out combined with controlled access to water in reducing EIPH in racing.

The *Paulick Report* first posted a story on the results of both studies Jan. 30.

According to the AAEP's 2017 Convention Proceedings document, the study by Dr. Knych of the Ken L. Maddy Equine Analytical Chemistry Laboratory looked at the efficacy of administering Lasix 24 hours out, instead of the current four hours out called for in racing's model rules. The study concluded that administering furosemide four hours before a race was more effective in reducing the severity of EIPH than going to 24 hours out.

The Knych study saw 15 Thoroughbreds administered furosemide either four or 24 hours prior to a five-furlong simulated race. Blood samples were collected before and after the simulated race for determination of furosemide, lactate, hemoglobin, and electrolyte concentrations.

One hour after the race, an endoscopic exam and bronchoalveolar lavage (BAL) was performed. Horses were assigned an EIPH score based on previously published criteria. The number of red blood cells in in BAL fluid was also determined.

"There was a statistically significant difference in EIPH scores between the four-hour and 24-hour furosemide administrations," the study determined. The study noted that none of the treatments prevented EIPH in the horses but that reducted red blood cell counts in bronchoalveolar fluid post-race indicated that administering furesomide four hours before a race was the most effective.

According to its introduction, the study came together following anecdotal reports that suggested furosemide administration 24 hours prior to strenuous exercise could be equally effective at decreasing EIPH.

The United States is one of the few countries that allows the raceday administration of Lasix. A study showing efficacy in preventing EIPH at 24 hours or beyond had potential to reshape current raceday policy of administration four hours before the race.

In the study led by Bayly, it was determined that a 0.5 mg/kg administration of furosemide 24 hours before strenuous exercise combined with controlled access to water shows potential for reducing the severity of EIPH.

The study used six horses who underwent treadmill exercise to fatigue after seven different protocols that

adjusted the dosage amount of the Lasix and timing of the administration. The study concluded that, "Furosemide, 0.5 mg/kg, combined with controlled access to water, significantly reduced the severity of EIPH," adding that, "No ill effects were detected in the horses."

In its AAEP presentation outline, the study noted that "Although the findings were promising, the number of horses used was small. The effects of furosemide on water and ion excretion were evident for 24 hours but did not adversely affect the horses, likely because of increased absorption of wager and ions from the colon."

In September 2015, Grayson Jockey Club Foundation announced it had launched funding of the two projects. The AAEP also played a prominent role in funding the projects, along with a number of racetracks.

Study Narrows Focus on How Furosemide Works

A recently published study in *Comparative Exercise Physiology* found a relationship between the administration of the medication furosemide, used to prevent exercise-induced pulmonary hemorrhage, and an enzyme that affects the pressure within the blood vessels in a horse's lungs.

The relationship potentially points toward new avenues to explore regarding the treatment of EIPH in Thoroughbred racehorses.

The study, conducted at Gávea Racecourse in Rio de Janeiro, Brazil, analyzed post-race blood samples from 73 horses over eight race days. Of the 73 horses, 47 had been treated with 250 mg of furosemide before their race and 26 were not medicated.

These samples were then tested for levels of angiotensin converting enzyme (ACE), a potent vasoconstrictor that when active contributes to higher blood pressure. Several studies have affirmed furosemide's effectiveness in reducing incidences of EIPH, but how the diuretic drug actually works is still unknown. This study showed ACE activity was significantly reduced in the horses that had been treated with furosemide.

"Multiple regression analysis demonstrated that pre-race furosemide significantly influenced ACE activity post-race, while distance raced, temperature, humidity, and hematocrit did not," the study concluded. "This is a novel finding which might impact on the search for the exact implications of furosemide use, and its effects on physiology and performance of Thoroughbred racehorses utilizing loop diuretics as treatments for EIPH."

The horses used in this study were already stabled at Gávea and the treated horses were part of the racetrack's established protocol on managing EIPH. At Gávea, a horse is entitled to pre-race furosemide if an official racetrack veterinarian has documented a bleeding episode through tracheobronchoscopy exam. A registered bleeder can receive furosemide four hours prior to post time and must continue to receive treatment for every race within 90 days from diagnosis. Horses that are younger than 3 1/2 years old are not allowed to receive pre-race furosemide, and any medicated horse is prohibited from competing in a group 1 or group 2 race.

While furosemide has proven to be the most effective method of reducing EIPH, the medication still does not entirely prevent its occurrence. In the Gávea study, 36.2% of the non-medicated horses showed some degree of post-race bleeding compared with 76.9% of the treated horses.

"This study confirms that, although furosemide might reduce EIPH severity after a single bout of exercise, it does not abolish or reduce its occurrence," wrote the study's authors. "This conclusion does not argue against the use of furosemide as a treatment for control of EIPH, but indicates the continuing need for better alternatives to limit the progressive and deleterious effects of repeated episodes of EIPH on the lungs of horses, and that further research into the possible role of renin-angiotensin aldosterone system components (like ACE) in developing new treatments is needed."

The study was published by Dr. Maria Fernanda de Mello Costa, Dr. Fernanda Aparecida Ronchi, Dr. Yoonsuh Jung, Dr. A. Ivanow, Dr. Juliana Braga, Dr. M.T. Ramos, Dr. Dulce Elena Casarini; and Dr. Ronald F. Slocombe.

RESEARCH ARTICLE

ACE activity post-race is influenced by furosemide administration

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Abstract

Exercise induced pulmonary haemorrhage (EIPH) affecting racehorses continues to raise questions regarding animal welfare and to-date no effective treatment has been identified. The mode of action of furosemide on EIPH, the only medication for the condition accepted in some racing jurisdictions, has not been completely elucidated. This research investigated the interaction between furosemide on angiotensin converting enzyme (ACE) as a potential pathway for future investigation of EIPH treatment options in a prospective case-control analytical study. ACE is a potent vasoconstrictor and substances reducing its activity could potentially contribute to decreasing blood pressure and EIPH. Horses racing on 8 official race days at Gávea Racetrack, Brazil had respiratory endoscopy data and blood samples collected after the race and were grouped into furosemide medicated and non-furosemide medicated horses. ACE measurement was conducted using fluorescence in a previously validated method. Environmental, race and haematological data were also recorded. A multiple regression model was used to analyse the data collected, with further analysis including Fisher's exact test and Pearson's chi-squared test with Yates' continuity correction; a Welch two sample t-test and a simple linear regression model. 73 horses were included in the study. ACE activity between horses not medicated and medicated with furosemide was significantly different. Pre-race furosemide significantly influenced ACE activity post-race, while distance raced, temperature, humidity, and haematocrit did not. Horses medicated with pre-race furosemide still demonstrated some degree of bleeding after the race and were at higher risk of presenting EIPH than non-medicated horses. Horses medicated with furosemide have lower circulating ACE activity which might indicate a protective effect of furosemide. Furosemide might reduce EIPH severity after a single bout of exercise, but it does not abolish or reduce its occurrence.

Keywords: horse, exercise induced pulmonary haemorrhage, biomarkers