Minnesota Racing Commission

Statement of Need and Reasonableness

November 1, 2012

Upon request, this Statement of Need and Reasonableness can be made available in an alternative format, such as large print, Braille, or cassette tape, or digital disc. To make a request, contact Ms. Marlene Swanson at the Minnesota Racing Commission, P. O. Box 630, Shakopee, MN 55379; phone 952-496-7950, fax 952-496-7954; or email at *marlene.swanson@state.mn.us*. TTY users may call the Racing Commission at 800-627-3529.

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INTRODUCTION

The racing commission is considering rule amendments that will lower the threshold level for phenylbutazone from five micrograms to two micrograms of the substance or metabolites thereof per milliliter of blood plasma or serum in race horses older than two years old. No concentration of any level of a nonsteroidal anti-inflammatory drug (NSAID) would be allowed in the serum or plasma sample taken after a race from a two year old horse.

ALTERNATIVE FORMAT

Upon request, this Statement of Need and Reasonableness can be made available in an alternative format, such as large print, Braille, or cassette tape, or digital disc. To make a request, contact Ms. Marlene Swanson at the Minnesota Racing Commission, P. O. Box 630, Shakopee, MN 55379; phone 952-496-7950, fax 952-496-7954; or email at *marlene.swanson@state.mn.us*. TTY users may call the Racing Commission at 800-627-3529.

STATUTORY AUTHORITY

The Racing Commission's statutory authority to adopt the rules is set forth in Minnesota Statutes section 240.23, which provides: The Commission has the authority, in addition to all other rulemaking authority granted elsewhere in this chapter to promulgate rules governing a) the conduct of horse races held at licensed racetracks in Minnesota, including but not limited to the rules of racing, standards of entry, operation of claiming races, filing and handling of objections, carrying of weights, and declaration of official results, b) wire communications between the premises of a licensed racetrack and any place outside the premises, c) information on horse races which is sold on the premises of a licensed racetrack, d) liability insurance which it may require of all racetrack licensees, e) auditing of the books and records of a licensee by an auditor employed or appointed by the Commission, f) emergency action plans maintained by licensed racetracks and their periodic review, g) safety, security, and sanitation of stabling facilities at licensed racetracks, h) entry fees and other funds received by a licensee in the course of conducting racing which the Commission determines must be placed in an escrow account, i) affirmative action in employment and contracting by licensed racetracks, and j) any other aspect of horse racing or pari-mutuel betting which in its opinion affects the integrity of racing or the public health, welfare, or safety.

Further statutory rulemaking authority relating to the amendments contained herein includes M.S. 240.24, subd. 2, Medication as amended by Laws of 2012, Ch. 279, Section 3.

Under these statutes and session law, the Racing Commission has the necessary statutory authority to adopt the proposed rule amendments.

REGULATORY ANALYSIS

(1) **a description of the classes of persons who probably will be affected by the proposed rule, including classes that will bear the costs of the proposed rule and classes that will benefit from the proposed rule**

The amendments to definitions, Medications provide greater guidance in the use of therapeutic medications in race horses. Class C licenses for race horse owners and trainers will be affected, a positive laboratory test showing any level above the permitted regulatory limit will result in a fine or some other penalty (loss of purse, license suspension) to be determined by the Stewards or Judges. The betting public, jockeys, drivers and horses will benefit in that horses will not be racing with performance enhancing medications in their system.

(2) the probable costs to the agency and to any other agency of the implementation and enforcement of the proposed rule and any anticipated effect on state revenues

There is no anticipated change in costs to the Commission or to any other state or local agency due to these proposed amendments. The Commission currently tests for these substances, so there should be no increased cost.

(3) a determination of whether there are less costly methods or less intrusive methods for achieving the purpose of the proposed rule

The proposed rule amendments do not change any standard operating procedures in the taking of samples by veterinary staff or testing method that the Commission is currently performing through its testing laboratory.

(4) a description of any alternative methods for achieving the purpose of the proposed rule that were seriously considered by the agency and the reasons why they were rejected in favor of the proposed rule

There are no better alternative methods for the amendments to horse medication. The Commission currently tests for the presence of these substances and will continue to do so. These amendments provide regulatory levels that can be used by horsemen and women and veterinarians when treating horses.

(5) the probable costs of complying with the proposed rule, including the portion of the total costs that will be borne by identifiable categories of affected parties, such as separate classes of governmental units, businesses, or individuals

Costs for sample collection by veterinary staff and laboratory testing costs for medication violations are currently part of the Commission's budget. These costs are reimbursed by its licensed racetracks. No governmental units will be affected. Individual horse owners or trainers will be affected only if testing exceeds the regulatory levels contained in these amendments (fines, loss of purse, or license suspension).

(6) the probable costs or consequences of not adopting the proposed rule, including those costs or consequences borne by identifiable categories of affected parties, such as separate classes of government units, businesses, or individuals

With the proposed amendments to medications, the Commission desires to provide the horsemen and women with guidance regarding the use of this medication. Not adopting the rule may result in confusion with medication administration as horsemen/women move from state to state. It may also result in an increased number of 2 year old racehorses that are infirm or unsound as a consequence of repeated use of this medication.

(7) an assessment of any differences between the proposed rule and existing federal regulations and a specific analysis of the need for and reasonableness of each difference

There are no current federal rules regarding the establishment of regulatory limits for this medication.

PERFORMANCE-BASED RULES

The Commission's mission statement states, "The Minnesota Racing Commission was established to regulate horse racing and card playing in Minnesota to ensure that it is conducted in the public interest, and to

take all necessary steps in ensuring the integrity of racing and card playing in Minnesota thus promoting the breeding of race horses in order to stimulate agriculture and rural agribusiness." These proposed rule amendments affect horse racing and are being proposed as means to strengthen the Commission's statutory authorized regulatory oversight so as to ensure the continued integrity of this form of legalized gambling. Any actual occurrence or even the perception that the integrity has been compromised would have a disastrous effect on not only the racetracks but also those that compete at the racetracks, many of whom rely on this activity for their livelihood. In proposing rule amendments, not only in this case but in all others as well, the Commission and its staff, constantly strive to be aware of ways by which the integrity of racing and pari-mutuel wagering can be improved and strengthened while at the same time proposing rules that allow flexibility by racing participants and Commission staff in responding to unanticipated situations in a business like fashion. This is done during the conduct of regulatory duties and responsibilities on a day to day basis and by staying current on national issues, especially medication issues, with regard to these proposed amendments.

ADDITIONAL NOTICE

These proposed amendments were discussed at regularly scheduled Commission meetings, Commission Work Sessions, or Commission Committee meetings. All rules discussion was clearly included on all agenda duly prepared and mailed or e-mailed 7 days prior to these meetings. Agendas were also posted on the Commission's website. The meetings were held on November 17, 2011, June 13, 2012, June 21, 2012, October 15, 2012, and October 18, 2012. Minutes from the full commission meetings are available on the Commission's website at www.mrc.state.mn.us. A special meeting of the Racing Committee was held at the Canterbury Park backside chapel with horse owners, trainers, and any other interested parties on August 1, 2012 to discuss the rule proposal.

The Racing Commission began work on the rules proposals in November 2011 and has provided updates on the status of the rulemaking proceedings at its monthly meetings. Continued updates were provided as needed during the course of the formal rulemaking process.

The Commission's Rulemaking Docket, which is publicly posted in the Commission's office as well as on the Commission's website, will be updated as necessary to reflect the status of these rules.

Our Notice Plan includes:

1. Publishing the Request for Comments in the July 2, 2012 edition of the State Register.
2. Posting the Request for Comments and the language of the proposed rules on the Commission's website.
3. Mailing or e-mailing the Request for Comments to Class A & B licensees as well as horsemen's organizations that are affected by horse racing in Minnesota, including the Minnesota Thoroughbred Association, the Horsemen's Benevolent and Protective Association, Minnesota Harness Racing, Inc., the Minnesota Quarter Horse Racing Association, the Jockey's Guild, and the United States Trotting Association.
4. Mailing or e-mailing the Request for Comments to organizations in Minnesota identified as having an interest in animal health including the Minnesota Board of Animal Health, the Minnesota Humane Society, the Minnesota Veterinary Medical Association, and the University Of Minnesota College Of Veterinary Medicine.
5. Our Notice Plan also includes giving notice required by statute. We will mail the rules and Notice of Intent to Adopt to everyone who has registered to be on the Commission's rulemaking list under Minnesota Statutes, section 14.14, subdivision 1a. We will also give notice to the Legislature per Minnesota Statutes,

section 14.116. The Proposed Rules and the Notice of Intent to Adopt will also be published in the State Register.

6. The Commission will provide a copy of the rules and Notice of Intent to Adopt Rules to Class A & B licensees, horsemen's organizations, and animal health organizations in Minnesota as noted in #3 and #4.

CONSULT WITH MMB ON LOCAL GOVERNMENT IMPACT

As required by Minnesota Statutes, section 14.131, the Department will consult with the Minnesota Management and Budget (MMB)). We will do this by sending the MMB copies of the documents that we send to the Governor's Office for review and approval on the same day we send them to the Governor's office. We will do this before the Commission's publishing the Notice of Intent to Adopt. The documents will include: the Governor's Office Proposed Rule and SONAR Form; the proposed rules; and the SONAR. The Department will submit a copy of the cover correspondence and any response received from Minnesota Management and Budget to OAH at the hearing or with the documents it submits for ALJ review.

DETERMINATION ABOUT RULES REQUIRING LOCAL IMPLEMENTATION

As required by Minnesota Statutes, section 14.128, subdivision 1, the agency has considered whether these proposed rules will require a local government to adopt or amend any ordinance or other regulation in order to comply with these rules. The Commission has determined that they do not because all activity that these amendments affect occur on licensed racetrack grounds, not out in the local community. There are times where we may have to contact local law enforcement or county/city attorney offices, but that is in the normal course of fulfilling our duties and responsibilities when events warrant. It is not anticipated that these amendments will either increase or decrease those contacts.

COST OF COMPLYING FOR SMALL BUSINESS OR CITY

Agency Determination of Cost

As required by Minnesota Statutes, section 14.127, the Racing Commission has considered whether the cost of complying with the proposed rules in the first year after the rules take effect will exceed $25,000 for any small business or small city. The Racing Commission has determined that the cost of complying with the proposed rules in the first year after the rules take effect will not exceed $25,000 for any small business or small city.

LIST OF WITNESSES

If these rules go to a public hearing, the Racing Commission anticipates having the following witnesses testify in support of the need for and reasonableness of the rules:

1. Ms. Mary Manney, Deputy Executive Director of the Commission will testify about the development and content of the rules.
2. Dr. Lynn Hovda, Chief Veterinarian of the Commission will testify about the development and content of the medication and testing proposals.

Ms. Marlene Swanson, Rules Coordinator will testify about the development and processing of these rules.

RULE ANALYSIS

Minnesota Statutes, chapter 14, requires the Commission to explain why a rule amendment is needed and why the amendment is the correct choice. The following analysis will explain why each amendment is needed and why it is a reasonable response with a rational basis. The need for and reasonableness of the proposed rules, amending Minnesota Rules part 7890.0100 is as follows:

***Minn. Rules*, part 7890.0100 Definitions, Subp. 13 Medication, A. Nonsteroidal anti-inflammatory drugs (NSAIDs).**

There are two parts to this rule change. Part 1 deals with lowering the permitted post race level of phenylbutazone in the horse's system from 5 ug/ml of serum or plasma to 2 ug/ml of serum or plasma. Part 2 deals with not permitting any post race level of any NSAID other than phenylbutazone in the serum or plasma of a 2 year old race horse.

PART 1:

Need: The Minnesota Racing Commission (MRC) attempts to comply with Model Rules put forth by the Racing Commissioners International (RCI). Model rules are proposed and executed based on input from groups such as the Racing Medication Testing Consortium (RMTC), Thoroughbred Racing Association (TRA) and others. This is done in an attempt to provide the horsemen with similar rules and regulations as they move from state to state and prevent confusion that accompanies different medication policies in different states.

Reasonableness: Phenylbutazone is a non-steroidal anti-inflammatory drug (NSAID) with analgesic (pain relieving), antipyretic (temperature lowering) and anti-inflammatory properties. It is widely used in equine veterinary medicine to treat medical conditions associated with soft tissue, muscle, bone, and joint pain.[1] Currently, phenylbutazone is a permitted medication in Minnesota with post race levels not to exceed 5 ug/ml serum or plasma of either phenylbutazone or oxyphenbutazone, the major metabolite.

1. In March of 2010, Dr. Rick Arthur, Chairperson of the Racing Medication & Testing Consortium (RMTC) Scientific Advisory Committee, recommended to the RMTC Board of directors that the post race level of phenylbutazone in horses be lowered from 5 ug/ml of serum or plasma to 2 ug/ml of serum or plasma.[2,3] This was done after the Racing Commissioners International (RCI) Regulatory Veterinarian Committee expressed concern that elevated levels of phenylbutazone at the time of prerace inspection masked signs of inflammation and injury and compromised their examinations.[3,4] The regulatory veterinarians based their concerns on the fact that horses are unable to speak and cannot tell them if and where they are sore. Examinations are generally performed 12-16 hours prior to scheduled race times and the level of phenylbutazone at that time is well elevated, especially if the horse has received phenylbutazone for several days in a row.[5] The request for a change was supported with data from Kentucky and California documenting elevated levels of phenylbutazone at prerace time as well as that from Iowa showing catastrophic breakdown statistics when phenylbutazone permitted levels were 2.2 mg/ml versus 5 ug/ml.[2,6] This is further supported by a scientific review provided by Dr. Larry Soma.[1]

The RCI Board of Directors in October 2010 voted 16-0 to lower the permitted post-race level of phenylbutazone to 2 ug/ml.[7] This move was supported by many groups associated with equine welfare including the American Association of Equine Practitioners (AAEP), The Jockey Club, The Jockeys' Guild, and the Thoroughbred Owners and Breeders Association (TOBA).[7,8] The Pennsylvania Racing Commission lowered the level of phenylbutazone to 2 ug/ml on September 15, 2010 followed by other states.[9] Currently of the 20 states affiliated with the National Thoroughbred Racing Association (NTRA) 12 have lowered their level

to 2 ug/ml, 3 are under review (Louisiana, Minnesota and West Virginia), 2 have lowered the level for graded states (Arkansas, West Virginia), and 4 remain at 5 ug/ml.[10] Effective January 1, 2012 the American Graded Stakes Committee lowered the level of phenylbutazone to 2 mcg/ml for all graded stakes races.[11] On August 31, 2012, the Kentucky Horse Racing Commission (KHRC) when lowering their level from 5 ug to 2 ug/ml provided dosage information to assist horsemen/women with the transistion.[12] Similar to Dr. Soma's review, the KHRC recommends that each horse be treated as an individual and that dosing be adjusted based on weight and administration time.[1,12] The Kentucky change from 5 to 2 ug/ml was supported by the RMTC in an August 30, 2012 news release. [13]

PART 2:

Need: The MRC attempts to promote the safety and well being of racehorses in Minnesota. This includes 2 year old horses, the youngest and most vulnerable group. They are generally stressed by the change in location, feed, training, and medication. Approximately 95% of 2 year old racehorses in Minnesota train and race with a nonsteroidal anti-inflammatory drug (NSAID) in their system. It is not unusual for racehorses to train on ketoprofen or flunixin and switch to phenylbutazone for race day administration. The underlying question is why stacking such as this occurs.

Reasonableness: Statistics show that in the United States less than 60% of 2 year old horses in race training ever actually race and less than 80% that raced as 2 year olds continue to race as a 3 year old.[14] Musculoskeletal injuries are an important factor as are breeding, conformation, and the increased use of drugs.

Some amount of training and racing in two year olds does not appear to be harmful to them and is endorsed by the AAEP and other groups.[8] Not all 2 year old race horses, however, are actually 2 years old, and many begin training and racing as young as 18-20 months. These horses are not physically or skeletally mature and several of their growth plates have not yet converted to bone. [15] Many of the 2 year olds in race training succumb to musculoskeletal injuries, especially bucked shins, bowed tendons, splints, and traumatic fetlock (ankle) joint injuries.[15, 16] Injuries in this age group are not necessarily acute in nature but associated with a repetitive, overuse motion.[16, 17] Phenylbutazone and other NSAIDS are frequently used in the treatment of these disorders to allow the horse to continue training and racing when, in fact, time off may be the best medicine. Further, the administration of different NSAIDs prior to race time may mask these pre-existing injuries resulting in continued damage, unsoundness, and loss of a horse, rider, or driver's life.[1, 17, 18]

Historically, phenylbutazone was not allowed in 2 year old racehorses but as medication rules became more permissive this was changed. This was followed several years later by the addition of two other NSAIDS (flunixin and ketoprofen). The MRC seeks to protect the 2 year old racehorses, our youngest and most vulnerable group, from the overuse of NSAIDS by allowing only phenylbutazone to be present in the post race sample in a level of 2 mcg/ml serum or plasma.

CONCLUSION

Based on the foregoing, the proposed rules are both needed and reasonable.

Date

Marlene Swanson
Rules Coordinator
Minnesota Racing Commission

End Notes

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16. Burba JB. The dilemma of bucked shins in the racehorse. www.equine.vetmedlsu%20shins.pdf. Accessed 8/17/2012.
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J. vet: Pharmacol. Therap. doi: lO.IlIl/j.1365-2885.2011.01299.x

The use of phenylbutazone in the horse

EXHIBIT 1

L. R. SOMA·
C. E. UBOHt &
G. M. MAYLINt

"School of Veterinary Medicine, University of Pennsylvania, P *A, USA; Pennsylvania EquineToxicology* & *Research Center, Department of Chemistry, West Chester University, West Chester, PA, USA;* tNew *York Drug Testing and Research Program, Morrisville State College, Ithiaca, NY, USA*

Soma, L. R., Uboh, C. E., Maylin G. M. The use of phenylbutazone in the horse. J. *vet. Pharmacol. Therap.* doi: 1O.1l11lj.1365-2885.20l1.01299.x.

This review presents a brief historical prospective of the genesis of regulated medication in the US racing industry of which the' nonsteroidal anti-inflammatory drug (NSAID) phenylbutazone (PBZ) is the focus. It presents some historical guideposts in the development of the current rules on the use of PBZ by racing jurisdictions in the US. Based on its prevalent use, PBZ remains a focus of attention. The review examines the information presented in a number of different models used to determine the effects and duration of PBZ in the horse. They include naturally occurring lameness and reversible-induced lameness models that directly examine the effects and duration of the administration of various doses of PBZ. The review also examines indirect plasma and tissue models studying the suppression of the release of arachidonic acid-derived mediators of inflammation. The majority of studies suggest an effect of PBZ at 24 h at 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not perform a prepurchase lameness examination unless the horse is free of NSAID. This remains the opinion of many regulatory veterinarians responsible for the prerace examination of race horses that they wish to examine a horse without the possibility of an NSAID interfering with the examination and masking possible musculoskeletal conditions. Based on scientific studies, residual effects of PBZ remain at 24 h. The impact of sustained effect on the health and welfare of the horse and its contribution to injuries during competition remains problematic.

(Paper received 26 July 2010; accepted for publication 20 March 2011) *Lawrence R. Soma, School of Veterinary Medicine, University of Pennsylvania, 382 West Street Rd., Kennett Square, PA, USA. E-mail: soma@vet.upenn.edu*

EXHIBIT 1

HISTORICAL PROSPECTIVE

Phenylbutazone (PEZ) is second only to aspirin as one of the oldest nonsteroidal anti-inflammatory drugs (NSAIDs). It was introduced into veterinary medical practice in the 19 50s and still remains one of the more commonly used NSAIDs in the horse (Tobin *et al* .. 1986). In 1959 it was approved for use in racing by the State of Colorado and some attribute this ruling as the beginning of the era of controlled medication in racing (Tobin, 1981). PEZ became news worthy in 1968 when Dancers' Image won the Kentucky Derby and the postrace urine tested positive for PBZ. By the early 1970s it was legalized in most states and became *well* established by the mid 1970s (Gowen & Lengel, 1993). In some racing jurisdictions as long as the sum of the combined urine concentration of PBZ and its metabolite, oxyphenbutazone (OPBZ), did not exceed a prescribed concentration, the horse was not in violation of the medication rules, In 1977 the National Association of State Racing Commissioners Veterinary-Chemist Advisory Committee concluded that 'PBZ does not change a horse's innate ability to race. *but* by relieving inflammation it may enable the horse to race closer *to* maximum capabilities' (Gabel *et al.*, 19Z7). In the late 1979, the use of PBZ came under scrutiny which resulted in the publication of the book 'The Misuse of Drugs in Horse Racing: a Survey of Authoritative Information on Medication of Race Horses' by the Illinois Hooved Humane Society. This publication stirred controversy on the use of PBZ especially on race day and many jurisdictions revised their rules on race day use of PBZ .. In 1982 a Committee appointed by the National Association of State Racing Commissions recommended 2 ug/mL as the decision or .regulatory plasma/serum concentration of PEZ. Thin layer chromatography was the primary method of drug screening in urine at this time. This proposed concentration (2 µg/mL) was based on the concerns of racing chemists that high PBZ blood concentrations would produce urinary PBZ and metabolites that would interfere with or 'mask' detection of other drugs (Gabel *et aI.*, 1977). Further studies indicated that the 'masking effect' was not a concern (Woods *et al.*, 1985a,b, 1986; Tobin *et aI.*, 1986) and the upper plasma/serum threshold concentration was increased to 5 *ug/mL.* Complete uniformity does not exist among racing jurisdictions many have remained at 2 *µ/mL* and others are at 5 *µg/mL,* or at some concentration in between.

CLINICAL OPINIONS ON THE USE OF PBZ

Phenylbutazone is considered valuable drug in the training of sore horses to maintain fitness in those with early joint or ligament problems. The use of an NSAID such as PBZ enables a horse to continue training or return to training in a shorter period. On the other hand a major drawback to the use of PBZ is the veterinarians' inability to evaluate the degree of lameness with this medications present in the horse's system (Cannon, 1973). It was also the opinion of many veterinarians that PBZ would allow a horse to compete with mild chronic arthritic changes. but did not possess sufficient anti-inflammatory activity to allow a horse with a serious injury to compete. The NSAID can be used to restore normal performance in a horse debilitated by some injury to joints, tendons, or muscle achieved by its anti-inflammatory actions and relief of pain. The short-term effects are not in doubt, but the long-term merits of continuous administration of PBZ in many cases are problematic. The cynical remark that some therapies, such as corticosteroids and NSAID allow the patient to walk to the postmortem room is an overstatement but the veterinarian must consider the long-term effect of therapy and that resting the horse may be the best approach (Sanford. 1983). Many veterinarians consider the use of NSAID justified in show-horses. show-jumpers, and combined training and have presented opinions on the use of PBZ based on the activity of the horse (Dunn. 1972). The United States Equestrian Federation rules allow higher concentration during competition compared to racing industry rules. There is great therapeutic value in the use of PBZ in the treatment of acute 'inflammatory conditions or in older horses in a nonraclng environment for the treatment of chronic osteo-arthritis where it can extend the useful life of the horse (Barragry, 1973).

A moral dilemma confronts the practicing veterinarian when prescribing PBZ or other medications for the treatment of the varied musculoskeletal condition in competition horses especially race horses; will the medication allow a horse to maintain a training schedule thereby allow the animal to function or is the medication contributing to further injury to the detriment of the horse? This is especially true In younger horses with a fresh injury and an unsuspecting owner administering an NSAID and inflicting further damage. Many veterinarians agree that the use of anti-inflammatory drugs could mask unsoundness in horses being examined in a prepurchase examination for soundness (Dunn, 1972). NSAIDs including PBZ. have masked clinical signs that have resulted in *cecal* perforation *{Rosset* al.,1985).Masking of existing musculoskeletal condition is the concern of regulatory veterinarians who are examining horses on a daily basis knowing that the examination is not in a medication-free horse.

In a multi centre field study, PBZ and suxibuzone, a prodrug of PBZ, were equally effective in the treatment of a number of acute. chronic, nonspecific lameness in which all horses were consistently lame upon trotting, Approximately 50% of the horses showed an improvement within 3 days of treatment with 30% showing an additional improvement at 6 days (Sabate *et al.,* 2009). This study illustrated the concern of many veterinarians as to the duration of administration of PBZ: if Significant improvement had not occurred within 4-5 days re-evaluation should be performed (Ieffcott & Colles, 1977; Reilly. 2000).

Toxicity of PBZ in the horse and ponies has been reviewed and several factors may predispose towards PBZ toxicity in the horse. including breed and age. but high dose is considered to be particularly important (Lees & Higgins. 1985). Clinical experience suggests that PBZ can be administered to horses in modest doses for a prolonged period of time without detectable side-effects. (Tobin *et al* . 1986). Blood dyscrasias commonly described in man have not been reported in the horse and despite the lack of documented evidence. toxicity of PBZ in the horse is considered to be lower than that in human. PBZ should not be administered if there are signs of gastro-intestinal ulceration. clotting defects or any cardiac, renal or hepatic dysfunction (leffcott & Colles, 1977). Despite the apparent lack of toxicity. adverse effects on the gastrointestinal track have been reported when administered at high doses (Karcher *et aI* .• 1990; Meschter *et al* .• 1990a,b). Possible toxic effects of NSAID are not limited to PBZ. Multiple daily administration of therapeutic doses of ketoprofen (2.2 mglkg). flunixin meglumine (1.1 mglkg). or PBZ (4.4 mg/kg) i.v., every 8 h. for 12 days produced changes In the glandular portion of the stomach: that was the area of the gastrointestinal tract most severely affected. Results of CBC. serum biochemical analyses. and fecal occult blood tests were not different from those of control horses with the exception of PBZ-treated horses that had a significant decrease in serum *total* protein and albumin concentrations.{MacAllister *et al., 1993).* Moderate to severe ulcerative colitis was diagnosed during necropsy, exploratory celiotomy, and biopsy; it was concluded that the ulcerative lesions may have gone unreported due to the anti-inflammatory effects of NSAID (Karcher *et aI.,* 1990). Renal papillary necrosis has been reported in horses to which PBZ was administered (Gunson, 1983) and medullary crest necrosis was reported in horses placed on maintenance doses of PBZ (Read 1983). Renal crest necrosis has also been reported in horses to which flunixin and PBZ were administered (MacAllister *et al.,* 1993). In horses on daily doses of 8.8 mg/kg for 21 days plasma albumin concentrations decreased significantly from days 10 to 21. treatment also caused neutropenia. No other clinical or hematologic abnormalities were detected for PBZ or control horses (McConnico *et al.,* 2008). A retrospective study of 269 horses administered ≤ 8.8mg/kg/day PBZ for 4 days or the lower dose of 2-4 mg/kg of body weight/day for up to 50 days remained clinically normal (Collins & Tyler. 1984).

The current lack of toxicity and observable side effects were based on the realization that the loading dose (4.4 mg/kg twice for 4 days) recommended by the manufacturer could be reduced. A revised schedule of 4.4 mg/kg twice daily for 1 day followed by 2.2 mg/kg twice daily for 4 days, then 2.2 mg/kg daily or as needed increased the margin of safety as no changes in clinical biochemistry or hematology were observed (Taylor *et al* .. 1983b). This modified dose regimen did not compromise clinical efficiency (Taylor *et* al., 1983a). The American Association of Equine Practitioners recommends a dose of 2.2 mg/kg daily with the last dose not more than 24 h prior to post time (Harvey, 1983). Clinical use of PBZ for many years suggests that with

adequate care, hydration, and the use of the lower therapeutic doses of FBZ can be used safely without clinically detectable side effects, The exception is the administration of a combined treatment of FBZ with f1unixin to horses as detrimental effects 'may outweigh any potential benefits. Gastroscopy of four horses revealed substantial gastric ulcers when administered the combination (Reed *et al., 2006).*

7.

In the equine, a dose-finding study for PBZ has not been reported, that is the evaluation of the improvement in clinical conditions at various doses. The current dose schedules are based on years of clinical use by many or administered doses to meet regulatory requirements of the industry. Based on the opinions and observations of veterinarians, investigators conducted a number of studies to determine the plasma PBZ concentrations 24 h following various dosing schedules, formulations, and dosages (Soma *et al* .• 1983; Chay *et ol., 1984;* Houston *et al* .. 1985; Soma *et al* .. 1985), Following completion of these studies, the recommended dosing schedule was as follows: oral administration of 4.4 mg/kg (2 g) for 3--4 days followed by a single i.v. dose of 4.4 mg/kg 24 h prior to racing. If these dosing recommendations were .followed, plasma PBZ concentrations on race day should not exceed 5 µg/mL. However, these studies did not attempt to determine the pharmacological effect of PBZ at 24 h or the pharmacological effects of a plasma concentration of 5 µg/mL, and this was the major drawback in the studies.

A prime consideration in the continuous use of PBZ or other NSAIDs is the possible contribution to catastrophic and noncatastrophic injuries. In the human sport medicine, which also applies to the veterinary field, there is a lack of high quality evidence to guide practitioners in their use and the possible adverse effects that have clinical relevance. Potential negative consequences on long-term use and the healing process are slowly growing (Fournier *et al.,* 2008). Specifically, NSAIDs are not recommended in the treatment of fractures, stress fractures or chronic muscle injury. The only exception may be very short-term use for analgesic purposes or as an adjunct to other analgesics. Judicious use of NSAID may be more appropriate in the management of acute muscle and ligament sprains, tendinitis, and muscle injury. However, length of treatment should always be kept as short as possible (Mehallo *et al., 2006).*

Cyclooxygenase activity is involved in the healing of many skeletal tissues, either directly or indirectly through modulation of the inflammatory response. Consequently, pharmacological manipulation of cyclooxygenase using NSAID can profoundly affect skeletal health. All of the NSAIDs should not be painted with a broad brush as having negative effects on healing and recovery of all types of injuries. In particular, NSAID use does not appear to have a long-term negative effect on tendons and ligaments and NSAID therapy may inhibit adhesion formation during tendon healing. which leads to a better functional recovery (O'Connor *et al.,* 2008). There is limited information on the use of PBZ and other NSAID on healing and synovial membrane health in the horse and many of the studies were conducted *in vitro.*

Oral administration of PBZ for 14 days significantly decreased proteoglycan synthesis in articular culture explants from healthy horses; these authors suggested that PBZ should be used judiciously in equine athletes with osteoarthritis. because chronic administration may suppress proteoglycan synthesis and potentiate cartilage damage (Beluche *etaI.,* 2001). It has been suggested that the use of PBZ early in the postoperative period may interfere with bone healing (Rohde *et al* .• 2000). In horses with experimentally-induced osteoarthritis the use of a COX-2 inhibitor, diclofenac, induced significantly less radial carpal bone sclerosis and overall gross cartilage erosion, compared with PBZ. Results obtained suggest that diclofenac had both clinical sign-modifying and disease-modifying effects. Only clinical sign-modifying effects were detected in association with PBZ administration (Frisbie *et al., 2009).*

The effects of *NSAIDs.* including PBZ, were investigated on lipopolysaccharide challenged and unchallenged equine synovial membrane in terms of production of prostaglandins E_2 (PGE_2) and hyaluronan, viability, and histomorphologic characteristics. These investigators concluded that the commonly used NSAIDs suppress induced synovial membrane PGE_2 production without detrimental effects on synovial membrane viability and function (Moses *et al..* 2001). Results of studies have also suggested that hyaluronan and carprofen might exert an anti-arthritic action through stimulation of PG synthesis and there is possible justification for therapeutic administration of enantiomeric rather than racemic carprofen (Frean *et al.,* 1999). Others have also suggested that use of carprofen in osteoarthritis horses may induce beneficial changes in articular cartilage matrix (Armstrong & Lees. 1999).

Catastrophic injuries remain an unavoidable but public relations nightmare in the racing industry, despite the fact that injuries in athletic competition are expected. The immediate perception in racing is that the injury is drug-related, when in fact there are many horse-related and external factors that contribute to musculoskeletal injuries. One study did conclude that higher concentrations of PBZ and other NSAID did contribute to a higher incidence of racetrack injury (Dirikolu *et al* .• 2009). The plasma concentrations of PBZ in this report were higher than are currently allowed in most racing jurisdictions. Racing jurisdictions allow plasma concentrations of PBZ or f1unixin; therefore, many horses are competing at plasma concentrations near the allowable limits. About 20% of the plasma samples exceeded 5 µg/mL at time of prerace examination (R. Arthur. Personal communication). The question remaining is what are the long-term effects of the continuous use of a NSAID on the musculoskeletal health of the horse? Are the short-term benefits of allowing the horse to compete under the influence of an NSAID worth the long-term risks? The veterinarian does have a greater choice of NSAID than just PBZ for the treatment of osteoarthritis in horses (Goodrich & Nixon, 2006) and it is inevitable that a horse may have to compete on a residual concentration of drug used during training. It may be of benefit to the horse to expand the veterinarian's regimen of allowable residual concentration of a more diverse list of NSAID.

PHENYLBUTAZONE AND PERFORMANCE

Results from performance studies suggested that PBZ had no clear effect on the performance of normal, healthy horses (Sanford, 1974). Plasma concentration of prostaglandins were increased in human (Demers *et aI* .• 1981) and equine during exercise (Birks *et al.,* 1991; Mitten *et aI* .• 1995). These exercise-induced increases in cyclooxygenase activity were inhibited by the administration of PB, but PBZ did not produce detectable changes in systemic hemodynamic or acid-base variables in either standing or running horses (Hinchcliff *et al.,* 1994). In exercising horses, the effect of inhibition of cyclooxygenase activity on the hemodynamic responses were examined. Administration of PBZ abolished the exertion-induced increases in plasma 6-ketoprostaglandin F_1 alpha and TXB_2• PBZ treatment resulted in significantly higher heart rates and right atrial pressures than control. There was no effect of PBZ on carotid or pulmonary arterial pressures, oxygen consumption, carbon dioxide production, blood lactate concentrations, or plasma volume during exertion. These results suggest that cyclooxygenase products likely mediate or modulate some of the systemic hemodynamic responses to exertion in horses (Mitten *et 01.,* 1996), but there is no evidence that the administration of PBZ and/or the suppression of cyclooxygenase products alters performance. In a similar study, the administration of PBZ (4.4 mg/kg) to the horse did not show significant differences from control horses in heart rate, right atrial, and pulmonary vascular pressures during high speed treadmill studies (Manohar *et 01* .. 1996). Endurance-like exercise (12 km/h for 3 h) did not affect the kinetic disposition of PBZ and dexamethasone. The conclusion of these authors was that resting horses can be used for determination of pharmacokinetics as no differences were noted in the disposition kinetics and the plasma-concentration time curves for the horse when at rest or sampling during exercise (Authie *et al., 2010).*

NOCICEPTION (PAIN PERCEPTION)

Pain experience and expression is difficult to determine in the horse as it is influenced by many factors such as species, breed, individual variations, and environmental characteristics. Equally difficult to assess is the alteration of pain by analgesic drugs. Latency to the onset of flexion of the limb in response to a noxious thermal stimulus and heat-evoked skin twitch have been reliable and reproducible measures of pain threshold and a nociceptive end-point for analgesic studies in the horse (Kamerling *et al.,* 1985). Thermal-evoked skin-twitch reflex and thermal-evoked hoof withdrawal reflex have been used to compare analgesic activity of procaine. mepivacaine and PBZ. Compared to procaine and mepivacaine, PBZ failed to alter pain thresholds over 36 hours postadministration (Kamerling *et aI.,* 1984). This type of stimulation produces an acute pain response and can be objectively used to compare the duration of regionally administered anesthetic agents and other drugs used to reduce the perception of pain. In the horse, PBZ was indistinguishable from saline controls when using a thermal stimulus (Kamerling *et: 0l* .• 1983). PBZ was not an effective drug when used to block thermal and specific nociceptive pain stimuli.

POSTOPERATIVE PAIN

Postoperative pain can be considered primarily a nociceptive pain produced by trauma to tissues due to direct intervention and disruption of these tissues. Inflammation due to surgical trauma is a part of the pain response and the use of NSAIDs has been promoted for this purpose postoperatively. Minimal differences were noted between PBZ and placebo administration in a group of horses undergoing arthroscopic surgery (Raekallio *et al.* 1997). In a similar postoperative study. flunixin, PBZ or carprofen was administered intra-operatively just prior to the end of anesthesia. The time following surgery when additional analgesic drugs were required postoperatively were. 8.4, 11.7 and 12.8 h for PBZ, carprofen, and flunixin, respectively. Horses that were administered the opioids, butorphanol, during surgery needed significantly fewer analgesic agents postoperatively (Johnson *et al. 1993).*

In a double-blind, randomized. prospective study of human patients undergoing arthroscopic surgery, those who were administered a prostaglandin inhibitor (naproxen sodium) had significantly less pain, less synovitis, less effusion, and faster recovery (Ogilvie-Harris *et al.,* 1985: Rasmussen *et al., 1993)* than those without. In equally as large a prospective study, no advantages were observed over control group of patients when compared to physical therapy and administration of the NSAID. dlclofenac (Birch *et 0l* .• 1993).

The use of NSAID in combination with more potent opioids for high-intensity pain and the weaker opioids for moderate- to low-intensity pain has been the topic of numerous publications discussing emerging trends in pain management (Schug *et* a!.. 2007; Fischer *et al* .. 2008: Huang *et al.,* 2008; Layzell & Layzell, 2008). Despite the use of PBZ postoperatively on a routine basis. similar studies in the total management of postoperative pain using NSAID combined with the opioids are lacking in the equine. The role of NSAID in the management of postoperative pain was suggested in an early publication (Mather. 1992) and authors still suggest they may contribute to improved functional outcomes without Significant adverse effects (Reuben & Reuben, 2007).

CENTRAL NERVOUS SYSTEM EFFECTS AND CROSSING OF THE 'BLOOD-BRAIN BARRIER'

Phenylbutazone has no known spinal or central nervous system (CNS) effects that are involved in the suppression of pain. The effects are primarily thought to be peripheral in action without CNS action or any noticeable sedation. To exert a central effect, NSAIDs have to cross the blood-brain barrier. Transfer across the blood-brain barrier is controlled by simple physico-chemlcal factors. OPBZ. indomethacin. and ketoprofen are characterized by high lipophilicity. At steady state, their free plasma

concentrations correspond to their cerebral spinal fluid concentrations (Bannwarth *et al* .• 1989). The presence of these NSAIDs in the brain may explain the antipyretic properties and some side effects of the NSAID. Concentrations of OPBZ in spinal fluid are similar to corresponding concentrations of unbound free OPBZ in plasma, which is approximately 5% of the total concentration of OPBZ in plasma (Gaucher *et al.,* 1983). Similarly, cerebral spinal fluid concentrations of ketoprofen reflect the unbound plasma ketoprofen concentrations and were in equilibrium with the plasma concentration from 2 to 13 h after administration (Netter *et al.* 1985). Ibuprofen. flurbiprofen, and indomethacin rapidly cross the blood-brain barrier. Plasma protein binding limits the driving force for uptake of NSAID into the brain by reducing the free fraction of NSAID in plasma (Parepally *et al.,* 2006). The observation that long-term treatment of patients with ibuprofen results in a reduced risk: and delayed onset of Alzheimer's disease suggests that it crosses the blood-brain barrier, has a central effect, and reduces inflammation in the Alzheimer's disease brain (Dokmeci & Dokmecl, 2004). Attempts to correlate the CSF concentrations of indomethacin with its regional inflammatory suppression and analgesic activity have not been successful (Bannwarth *et al.,* 1989). The assumption that all NSAID relieve pain only through an inhibition of prostaglandins synthesis, have no antinociceptive effects, central effects, and ail actions are peripheral in nature have been challenged (McCormack & Brune. 1991).

PBZ IN SYNOVIAL FLUID

The efficacy of NSAIDs in joint diseases depends on their concentrations within the joint as the cells within the joint are the major site of action (Furst, 1985). There is no barrier to the diffusion of unbound NSAID into the joint cavity and their therapeutic effectiveness is determined by passage across the synovial membrane. which can depend on the degree of inflammation of the joint and on the pharmacokinetic properties of the drugs. Most NSAIDs are weak acids with a pK_a between 3 and 6 and the un-ionized forms are lipid soluble. The NSAID are primarily in the ionized form as the pK_a. values are much lower than the pH of blood. The proportion changes to un-ionized as the environment becomes more acidic as in the stomach, kidneys and more importantly inflamed tissues (Day *et al.. 1987).* Inflamed joints concentrate NSAID because the pH of the synovial fluid is much lower than noninflamed joints. For example, the synovial concentration of OPBZ was higher in human patients with severe inflammation than in those with no or little inflammation (Gaucher *et al.,* 1983). Similar observations were made in an inflammatory carrageenan rat paw model where the concentrations of C^{l}4pBZ was approximately 800-fold greater than plasma (Graf *et aI., 1975).*

NSAIDs are highly protein bound, but effect of protein binding on disposition into synovial fluid may not be a consideration, as bound drug will dissociate as fast as free drug diffuses. (Simkin. 1988). In inflammatory joint diseases, albumin-bound fraction diffuses better due to the increased capillary permeability to proteins; therefore. the concentration of the NSAID will be higher in inflamed tissues. (Netter *et al., 1989).*

NSAIDs are classified in two categories based on their half-lives. Drugs with a short half-life, shortly after administration, the concentration in synovial fluid was lower than in plasma but reversed as the plasma concentration declines. In the horse, ketoprofen was no longer detectable in plasma after 5 h whereas synovial fluid concentrations were detected for 8 h. In the same study, carprofen with a half-life 10 times longer than ketoprofen, the concentrations in synovial fluid were significantly lower that plasma at all time points (Armstrong *et al.,* 1999). In rheumatoid patients on chronic therapy this may be a possible reason for the drug's extended duration of action of drugs with apparent short elimination half-lives in plasma (Fowler *et al.,* 1983). On the other hand, drugs with a longer half-life such as PBZ, the peak concentrations in synovial fluid were lower than plasma, remained lower and decreased in parallel with the plasma concentration (Netter *et al.,* 1983). This difference in the pharmacokinetics based on elimination half-life was observed in horses with no joint disease. Following the i.v, administration of naproxen. synovial concentrations peaked at ~8 h: were lower and followed a parallel decline in plasma and synovial fluid concentrations for up to 36 h. There were no differences in the secondary disposition rate constant for plasma and elimination rate constants for the synovial fluid indicating a parallel decline in both concentrations of naproxen (Soma *et al.. 1995).* Although this study was not done for PBZ in the horse similar relationships would be expected as the pharmacokinetics are similar (Soma *et al., 1983).*

These differences based on the pharmacokinetic characteristics of the drug, delays in achieving synovial fluid concentrations and more importantly in assessing the effects of the administered drug to a diseased subject make it difficult to establish correlations between plasma concentrations and therapeutic response (Famaey, 1985). In human patients with osteoarthritis, the synovial fluid concentrations of PBZ were lower than plasma, with a good correlation between the two. In human patients with rheumatoid arthritis synovial PBZ concentrations were higher based on the greater inflammatory nature of the disease and a higher synovial fluid protein concentration (Farr *et al.,* 1982). In c1inico-pharmacological study in humans, a relationship was present between dose, plasma concentration, and clinical effects of PBZ (Brooks *et al .. 1975).*

Many authors have suggested that the plasma concentrations of NSAIDs, do not correlate well with assessments of therapeutic response. This may reflect weaknesses in experimental design, capability of determining the changes in pain levels and inflammation, and in clinical studies the variability in the diseases being studied. It may be that concentrations in plasma bear only a distant relationship to those in the inflamed tissues where NSAIDs, presumably act (Famaey, 1985; Grennan *et aI.,* 1985; Simkin, 1988). Compared with the CNS, NSAID readily penetrate into the joint and concentrations are not limited to the unbound fraction and will vary with the synovial environment. Studies in non-diseased joints are useful to describe the relative relationships and pharmacokinetics of the drug, but may have

little relationship in the diseased joint. Despite the many studies and years of its use in the horse, plasma synovial relationships in the non-diseased and naturally occurring diseased joint have not been reported.

NATURALLY OCCURRING OSTEOARTHRITIS

In a randomized controlled clinical trial, efficacy and safety of paste formulations of firocoxib (Equioxx®; Merial, Duluth, GA, USA) and PBZ in horses with naturally occurring osteoarthritis were compared. Horses were treated with firocoxib (0.1 mg/kg, orally every 24 h) or PBZ (4.4 mg/kg, orally every 24 h) for 14 days. Clinical improvement was defined as a reduction of at least 1 lameness score grade or a combined reduction of at least 3 points in scores for pain during manipulation or palpation; joint swelling, joint circumference, and range of motion. Results obtained suggested some greater improvement in some categories tested than others following firocoxib. but overall clinical efficacy of firocoxib and PBZ in horses were comparable (Doucet *et al., 2008).*

Horses with naturally occurring forelimb and hind limb lameness were exercised on a treadmill and the degree of lameness evaluated by the use of kinematic analysis while trotting on the treadmill. Horses entered into the study were judged to have AAEP lameness scores of 1-3 based on a scale of upper severity score of 5 (Ross. 2003). In a cross-over study, PBZ paste was administered at 2.2 mg/kg (orally every 12 h for 5 days), alone or in combination with fluntxin meglumine administered at 1.1 mg/kg, (i.v. every 12 h for 5 days). Lameness evaluations were performed before and 12 h after administration of two NSAID treatment regimens. Administration of a combination of the two NSAIDs alleviated lameness more effectively than did oral administration of PBZ alone. Based on the authors' conclusion, when evaluating all 28 horses, there was a significant clinical improvement after the administration of both drugs in all horses except five with forelimb lameness. PBZ alone did not result in significant clinical improvement in all horses. Results of this study suggested that the use of combinations of NSAID (stacking) did have a better effect at 12 h and would have a greater effect at 24 h. The authors suggested that 'stacking of drugs' should be a real concern (Keegan *et al*,. 2008).

The analgesic effects of PBZ in nine horses with chronic forelimb lameness were studied. The horses were administered saline for control or PBZ at 4.4 and 8.8 mg/kg i.v., daily for 4 d. Peak vertical force (force plate) was measured and AAEP clinical lameness scores were assigned before initiation of each treatment. All horses were evaluated 6, 12, and 24 h after the final dose. The vertical force was significantly increased at all post-treatment evaluation times after PBZ compared to control horses. Clinical lameness and vertical force scores were significantly decreased at 6 and 12 h at both doses and no differences were observed between the low or high dose. Scores were significantly decreased 24 hours after treatment only when PBZ was administered at the high dose (Hu *et al., 2005).*

Force plate analysis and the AAEP lameness scoring system were used to evaluate the analgesic efficacies of flunixin (1.1 mg/kg), PBZ (4.4 rug/kg), or physiologic saline solution administered i.v. in 12 horses with navicular syndrome. Medications were administered once daily for 4 days with a 14-day washout period between treatments. At 6, 12, and 24 h after the fourth treatment, AAEP lameness evaluations and force plate data indicated significant improvement in lameness from baseline values in horses treated with f1unixin or PBZ, compared with saline-treated control horses. The effect of f1unixin or PBZ was maintained for at least 24 h but no differences from control were noted at 30 h. Flunixin meglumine and PBZ appear to have similar analgesic effects in horses with navicular syndrome (Erkert *et al.. 2005).*

The analgesic effects of the NSAID, ketoprofen at 2.2 and 3.63 mg/kg and PBZ at 4.4 mg/kg were compared in seven horses with bilateral forelimb chronic laminitis. Hoof pain was quantified objectively by means of an electronic hoof tester and lameness was subjectively graded on a modified Obel scale (Obel, 1948). Ketoprofen administered at 3.63 mg/kg (equimolar to 4.4 mg/kg of PBZ) reduced hoof pain and lameness score to a greater extent than the 2.2 mg/kg dose of ketoprofen or the 4.4 mg/kg of PBZ. These data suggest that ketoprofen at 1.65 times the recommended therapeutic dose was more potent than PBZ in alleviating chronic pain and lameness in horses. PBZ (4.4 mg/kg) and high dose of ketoprofen were still effective at 24 h (Owens *et al . 1995).*

Horses (12) with navicular syndrome were fitted with 3° heel-elevation horseshoes and a force plate was used to measure baseline peak vertical ground reaction force of the forelimbs. Vertical force was measured 24 h and 14 days after shoeing and 24 h following the administration of PBZ (4.4 mg/kg, i.v. q 12 h) for 5 days. There was further significant improvement in vertical force measured 24 h following PBZ treatment. Heel-elevation shoeing alone and in combination with PBZ administration quantitatively decreased lameness in horses with navicular syndrome; injection of distal interphalangeal joint with triamcinolone acetonide did not significantly improve the vertical force measurements (Schoonover *et al . • 2005).*

INDUCED LAMENESS MODELS

The objective was to test the hypothesis that PBZ alleviates lameness in an adjustable heart bar-shoe model of equine foot pain following a single il.v. dose of 4.4 mg/kg. Heart rate and lameness score (1-5) were assessed every 20 min for 2 h and then hourly through 9 h. A lameness grade of four was produced for the study and no lameness was observed following the study when the setscrew was removed. In the PBZ-treated horses, the lameness score was lowest between 4 and 5 h post-treatment when the score was reduced from 4 to 1.5 compared with control horses. PBZ was efficacious in alleviating lameness in this model. The PBZ plasma concentrations were approximately 15 and 7 µg/mL at 4 and 8 h. respectively. The study period did not include observations beyond 9 h, but the lameness

score had not recovered to baseline values at that lime (Foreman *et al .• 2008).*

Lipopolysaccharide-induced synovitis was produced in horses and treated with PBZ (4.4 mglkg, i.v., q 12 h), or etodolac (23 mg/kg, i.v., q 12 h). Both reduced synovial fluid white blood cell counts at 6 and 24 h. In addition, both drugs significantly reduced PGE_2 levels at 6 h, but TXB_2 was only reduced by PBZ (Morton *et al .•* 2005). Using a standardized lameness model, flunixin was studied and PBZ was used in the same model as a positive control. At a dose of 4.4 mg/kg of PBZ and 1.1 mg/kg of flunixin peak effect occurred at 8-12 and 12 h, respectively. Flunixin analgesic activity persisted for 30 h and PBZ for 24 h (Houdeshell & Hennessey, 1977).

An induced arthritis model was developed to establish the relationship between the plasma concentration of PBZ and its pharmacological effects. A dose-effect relationship was shown for PBZ with an absence of effect for the 1 mg/kg dose and a maximum effect at about 2 mg/kg; at higher PBZ doses, the maximum effect was not modified, but its duration was increased from 8 h with a 2 mg/kg dose to about 24 h with an 8 mg/kg dose (Toutain *et al.,* 1994). This study and others cited in this review came to the same conclusion that the maximum dose was 2.2 mg/kg and higher doses did not increase the effect except the duration. Similar results were noted in humans, a dose-finding study determined that the most efficacious dose was 300 mg/day. Doses below this did not produce full benefit and no further improvement occurred with higher doses (Bird *et aI .• 1983).*

The production of muscle inflammation by the injection of Freud's adjuvant did not affect the plasma kinetics and when administered 5 weeks apart there was no within horse variability indicating that the administration of PBZ did not affect the plasma kinetics of subsequent doses (Mills *et. al .•* 1996). This was verified by clinical observations that the plasma concentrations in a large population of horses were consistent postrace when a routine administration schedule was established in a horse and previous administrations did not affect subsequent doses.

INDIRECT ASSESSMENT OF DURATION OF NSAID EFFECTS

It has been shown that the mechanism of the action of aspirin--like compounds was a direct inhibition of prostaglandin synthetase, thereby preventing prostaglandin biosynthesis (Vane, 1971: Moncada et *aI* .. 1974; Vane & Botting, 1987). Products of prostaglandin biosynthesis such as prostaglandins and prostacyclin produce hyperalgesia associated with inflammation and may cause pain in some inflammatory conditions by sensitizing the chemical receptors of afferent pain endings to other inflammatory mediators such as bradykinin and histamine. NSAIDs are potent inhibitor of the conversion of arachidonic acid to arachidonic acid-derived mediators of inflammation. The site of action of NSAID is the cyclooxygenase pathway, therefore, blocking the synthesis and release of several 'chemical mediators of inflammation. collectively krlown as eicosanoids. NSAIDs in normal therapeutic doses do not block the lipoxygenase pathways which may be responsible for the reduction of leukocyte migration into the inflammatory site and the reduction of edema (Higgs. 1980).

Cyclooxygenase (COX-I) was the first enzyme recognized for catalyzing the synthesis of prostanoids from arachidonic acid, since this initial description a second isoform COX-2 has been described. PBZ is primarily a non-selective COX inhibitor: *in vitro* analysis in horse blood showed a greater COX-l selectivity determined by the depression of TXB_2, compared to COX-2 selectivity determined by the depression of PGE_2 (Beretta *et al* .. 2005). This observation confirms that in the horse. PBZ is a more selective inhibitor of COX-l than COX-2. This is relevant in that species difference have been noted in the concentrations of the stable metabolite TXB_2 released by COX-l activation and the concentration of PGE_2 release by lipopolysaccharide activation of COX-2 and the selective inhibition by various NSAID (Brideau et ***a.*** *2001).*

There have been considerable advances in the development of pharmacokinetic/pharmacodynamic (PK/PD) models in veterinary and human medicine and investigators have studied the effects of the drug and concurrent changes in plasma or tissue concentrations of inflammatory mediators. Modem PK/PD studies link the effect(s) of the drug to its corresponding concentration in plasma (Lees *et al .•* 2004a,b,c; Toutain & Lees, 2004). General PD/PK models have been developed for describing drug actions on various active metabolites and hormones (Krzyzanski & [usko, 2001; Puchalski et *al .• 2001).*

A number of studies have used the reduction in the metabolic products of inflammation as indirect models of the actions of PBZ and other NSAIDs at the molecular level to determine the degree and duration of action. Three types of models have been used:

1. Suppression of the release of inflammatory mediators in blood samples. A number of PK/PD models have been developed using this technique (Lees *et al .•* 1987a; Soma *et al., 1992).*
2. Suppression of the release of inflammatory mediators in tissue cage and sponge models in which a sterile carrageenan solution was injected into the cage or sterile carrageenan-soaked polyester sponge strips were inserted subcutaneously. Both were based on the creation of a mild, reproducible and reversible inflammatory reaction that causes minimal distress to the experimental animals. The acute inflammatory exudates have been shown to contain proteins, white blood cells, and eicosanoids all because of the inflammatory reaction (Higgins & Lees, 1984; Lees & Higgins. 1984; Lees *et al.,* 1986; Higgins *et al .•* 1987a,b; Lees *et al.,* 1987a,b).
3. More recently, models in humans have used flow through methods to harvest inflammatory exudates. *In vivo* human bioassay can be used to study human volunteers and patients. Samples are collected from pertinent tissue sites such as the skin via aseptically inserted micro dialysis catheters. These experiments measured inflammatory substances in interstitial fluid collected from noninflamed and experimentally inflamed skin (Angst *et al .•* 2008a,b).

INDIRECT PLASMA MODELS

A study involving the inhibitory actions of NSAIDs on TXB_2 following a single dose of flunixin (1.1 mg/kg) or PBZ (4.4 mg/kg) was used to determine the duration of action of these drugs. Flunixin and PBZ produced similar degrees of reversible inhibition of TXB_2 at 4 (98% and 88%), 8 (77% and76%), and 24 (63% and 50%) h, respectively. At 48 h, inhibition of TXB_2 was no longer apparent (Lees et *01.,* 1987 a,b).

In a similar study, the concurrent administration of flunixin meglumlne (1.1 mg/kg, i.v.] and PBZ (2.2 mg/kg, i.v.) on the pharmacokinetics of each drug indicated that the pharmacokinetic variables calculated for each drug when administered alone and in combination were similar. Serum TXB_2 production was significantly suppressed for 8, 12, and 24 h after administration of f1.unixin and PBZ in combination. When these drugs were administered alone, the TXB_2 concentrations were not significantly different from control values at 24 h. Note in this study that the dose of PBZ was 2.2 mg/kg. (Semrad *et al., 1993).*

INDIRECT TISSUE MODELS

Distribution of PBZ and its active metabolite, OPBZ. into tissue fluids was studied by measuring concentrations in plasma, tissue-cage fluid, peritoneal fluid and acute inflammatory exudates harvested from a polyester sponge model of inflammation in ponies. PBZ and OPBZ readily penetrated into inflammatory sites. After 6 h. the concentration of PEZ was higher in exudates than in plasma and remained so at 24 h. Mean concentrations of OPBZ in all fluids were lower than those of PBZ at all times, but OPBZ readily entered body fluids, especially into inflammatory exudates: suggesting that OPBZ may contribute to the anti-inflammatory effect. The estimated elimination half-life of PBZ from exudates was 24 h compared to 5 h from plasma. The authors suggested that the persistence of PBZ and OPBZ in tissues exudates extended the duration of PBZ effectiveness (Lees *et. al.,* 1986). Other studies have shown that flunixin was also cleared more slowly from equine tissue inflammatory exudates than from plasma (Higgins *et al* .• 1987a,b).

Acute inflammation was induced in seven ponies by subcutaneous implantation of sterile carrageenan-soaked polyester sponge strips. Treatment comprised a single therapeutic dose of 4.4 mg/kg of PBZ administered intravenously at the time of sponge implantation. Exudates were harvested at 6, 12, and 24 h and examined for leukocyte and erythrocyte numbers. Leukocyte numbers were significantly increased from 6-h values at 12 and 24 h in both control and PBZ-treated animals but differences between control and treated ponies were not significant. The administration of PBZ produced Significant reductions in exudate concentrations of PGE_2 and 6-keto-$PGF_{1ct,}$ the stable products of prostacyclin at 6, 12, and 24 h. Concentrations of PBZ and OPBZ in exudates exceeded the plasma concentrations at 12 and 24 h. Concentrations of TXB_2, the stable products of TXB_2, were reduced in treated animals but these changes were not significant. Study results suggested an effect at 24 h based on the reduction of the two measured eicosanoids PGE_2 and 6-keto-PGF_{1ct} (Higgins *et al., 1984).*

In a 12-day treatment schedule, five ponies were administered an oral paste formulation of PBZ and five matched ponies were administered equivalent doses of a placebo paste. On day 12, a mild, nonimmune inflammatory reaction was induced subcutaneously. Exudates were collected at 4, 8, 12, and 24 h. There were no significant differences in exudate protein concentration and leukocyte numbers between the treatment groups, but exudate concentrations of 6-ketoFlor: were reduced at 4, 8, and 12 h and those ofTXB_2 at 8,12, and 24 h in the PBZ treatment group. The increases in surface skin temperature were significantly less in PBZ-treated than in placebo-treated ponies between 4 and 24 h (Lees & Higgins, 1986).

The most widely accepted mode of action for NSAIDs is inhibition of prostaglandin synthetase. Leukocyte and erythrocyte accumulation in exudates is part of the inflammatory process. In the tissue cage and exudates studies, this was not significantly affected by the NSAID (Lees & Higgins, 1984, *1986). In vitro* studies have shown that flunixin, PBZ, OPBZ. and indomethacin suppress leukocyte migration of which flunixin was the most potent of the drugs studied. The obvious difference between in *vivo* and in *vitro* studies is the more complex environment of the inflamed joint compared to the controlled environment of an in *vitro* study (Dawson *et al.,* 1987).

SUMMARY

This review presented a historical prospective and examined the information presented in four different models used to determine the pharmacological effects of NSAIDs, especially PBZ. They included naturally occurring lameness, reversible induced lameness, and indirect plasma and tissue models studying the suppression of the release of arachidonic-derived mediators of inflammation. The majority of studies suggest a persistent effect of PEZ at 24 h at 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not examine a horse for a prepurchase lameness examination unless the horse is shown to be free of NSAIDs and corticosteroids. Regulatory veterinarians responsible for prerace examinations of racehorses, wish to examine a horse prerace without the possibility of a NSAID or corticosteroid interfering with the examination and masking a possible musculoskeletal condition. Based on scientific reports and the impression of clinical veterinarians, residual effects of PBZ remain at 24 h. The impact of this sustained effect on the health and welfare of the horse remains problematic.

ACKNOWLEDGMENTS

This review was at the request of the Racing Medication and Testing Consortium. Medication Advisory Committee, and supported by the Pennsylvania Horse and Harness Racing Commissions and in part by the Pennsylvania Horsemen Benevolent and

Protective Association, Pennsylvania Harness Horsemen Associations and Meadows Standardbred Owners Association.

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~ Testing Consortium

TO: RMTC Board of Directors

FROM: Dr. Rick Arthur, Scientific Advisory Committee chairman

DATE: 4/12/10

SUBJECT: Background NSAID Recommendation

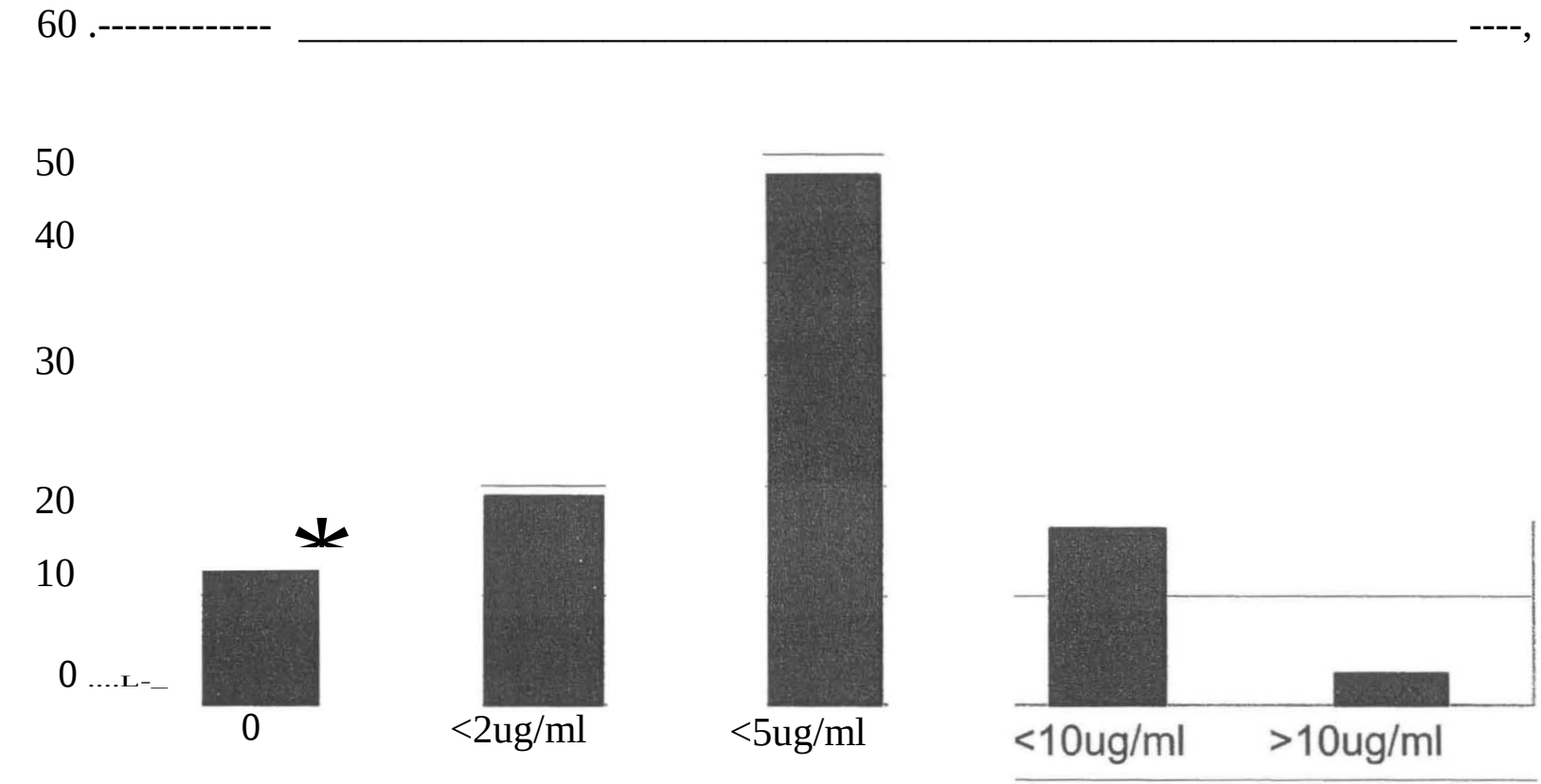
Last spring the ARCI Regulatory Veterinarian's committee submitted a letter to the RMTC and ARCI outlining their concern that current medication regulations were compromising pre-race examinations (attached Dr. David letter). Subsequently the RMTC Sci Adv committee asked Dr. Larry Soma to do a review of the scientific literature on phenylbutazone (PBZ). All members of the Sci Adv committee were encouraged to provide any comments to Dr. Soma. Attached is the final version after committee input (attached Soma review). Note the reviews conclusion:

> This review presented an historical prospective and examined the information presented in 4 different models used to determine the effects of NSAIDs, especially PBZ. They included naturally occurring lameness, reversible induced lameness, and indirect plasma and tissue models studying the suppression of the release of arachidonic-derived mediators of inflammation. The majority of studies suggest an effect of PBZ at 24 hours at a dose of 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not examine a horse for a pre-purchase lameness examination unless the horse is shown to be free of NSAIDs and glucocorticoids. This remains the opinion of many Commission Veterinarians in that they wish to examine a horse pre-race without the possibility of a NSAID or corticosteroid interfering with the examination and masking a possible musclo-skeletal condition. Based on scientific reports and the impression of clinical veterinarians, residual effects of PBZ remain at 24 hours. The impact of this sustained effect on the health and welfare of the horse remains problematic.

To obtain relevant data the blood samples were obtained from horses in CA & KY at exam time by CA & KY examining veterinarians (attached CA & KY Exam time samples).

The Sci Adv committee discussed all the information and the best options for PBZ regulation for the racing industry. IFHA rules, 48hr rules and other alternatives were discussed. The consensus was the best option was to revisit the 2ug/ml rule that was in place in many jurisdictions before the 5ug/ml rule was adopted. While this does not solve the problem identified by the ARCI Regulatory Veterinarian relative to pre-race examination, the conclusion was the 2ug/ml rule is a move in the right direction. There is a wealth of experience administering the 2ug/ml rule and until corticosteroids can be properly regulated, any more stringent PBZ rule will simply encourage more corticosteroid use. The general consensus was the latter would be more detrimental to horse health and welfare.

CA & KY Exam Time Samples (n= 214)



* Includes 7 samples in CA with flunixin in excess of regulatory threshold. The KY samples were not analyzed for flunixin)

PROPOSED CHANGES TO NSAID MODEL RULE

E. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

() The use of one of three approved NSAIDs shall be permitted under the following conditions:

(a) Not to exceed the following permitted serum or plasma threshold concentrations which are consistent with administration by a single intravenous injection at least 24 hours before the post time for the race in which the horse is entered:

(i) Phenylbutazone (or its metabolite oxyphenylbutazone) ~~– 5 microgrmas per milliliter~~ **2 micrograms per milliliter**;

(ii) Flunixin - 20 nanograms per milliliter;

(iii) Ketoprofen - 10 nanograms per milliliter.

(b) These or any other NSAID are prohibited to be administered within the 24 hours before post time for the race in which the horse is entered.

(c) The presence of more than one of the three approved NSAIDs, with the exception of Phenylbutazone in a concentration below ~~1 microgram per milliliter~~ **0.5 micrograms per milliliter** of serum or plasma or any unapproved NSAID in the post-race serum or plasma sample is not permitted. The use of all but one of the approved NSAIDs shall be discontinued at least 48 hours before the post time for the race in which the horse is entered.

(2) Any horse to which a NSAID has been administered shall be subject to having a blood and/or urine sample(s) taken at the direction of the official veterinarian to determine the quantitative NSAID level(s) and/or the presence of other drugs which may be present in the blood or urine sample(s).

PROPOSED CHANGES TO PENALTIES (NSAIDS)

LICENSED TRAINER	Phenylbutazone (2.1-4.9 meg/ml) Flunixin (21-99 ng/ml) Ketoprofen (11-49 ng/ml) Furosemide (>100 ng/ml) and no furosemide when identified as administered**	Phenylbutazone (≥5.O meg/ml) Flunxin (≥100 ng/ml) Ketoprofen (≥50 ng/ml) and CLASS C Violations
1 St Offense (365-day period) in any jurisdiction	Minimum fine of $250 absent mitigating circumstances	Minimum fine of $500 absent mitigating circumstances
2nd Offense (365-day period) in any jurisdiction	Minimum fine of $500 absent mitigating circumstances	Minimum fine of $1 ,000 and 15-day suspension absent mitigating circumstances
3rd Offense (365-day period) in any jurisdiction	Minimum fine of $1,OOO and 15-day suspension absent mitigating circumstances	Minimum fine of $2,500 and 30-day suspension absent mitigating circumstances
LICENSED OWNER	Phenylbutazone (2.1-4.9 meg/ml) Flunixin (21-99 ng/ml) Ketoprofen (11-49 ng/ml) Furosemide (> 100 ng/ml) and no furosemide when identified as administered**	Phenylbutazone (≥5.O mcg/ml) Flunixin (≥100 ng/ml) Ketoprofen (≥O ng/ml) AND CLASS.C VIOLATIONS
1 St Offense (365-day period) in any jurisdiction		Loss of purse. Horse must pass commission-approved examination before being eligible to run
2nd Offense (365-day period) in any jurisdiction		Loss of purse. If same horse, placed on veterinarian's list for 45 days, must pass commission-approved examination before being eligible to run
3rd Offense (365-day period) in any jurisdiction	Loss of purse. Horse must pass commission-approved examination before being eligible to run	Loss of purse. Minimum $5,000 fine, If same horse, placed on veterinarian's list for 60 days, must pass commission-approved examination before being eligible to run

RMTC Scientific Advisory Committee
Phenylbutazone Review
Lawrence R Soma, VMD
University of Pennsylvania
School of Veterinary Medicine
New Bolton Center Campus

Initial opinions on the effects of phenylbutazone (PBZ) and historical prospective.

Phenylbutazone was introduced into veterinary medical practice in the 1950s (Tobin et al., 1986) and still remains one of the more commonly used non-steroidal anti-inflammatory drugs (NSAID) in the horse. In the late 1970s, the use of PBZ came under scrutiny which resulted in the publication of the book "The Misuse of Drugs in Horse Racing: a Survey of Authoritative Information on Medication of Race Horses" by the Illinois Hooved Humane Society. This publication stirred controversy on the use of PBZ especially on race day. In 1977 the National Association of State Racing Commissioners Veterinary-Chemist Advisory Committee concluded that "phenylbutazone is a safe, effective nonsteroidal anti-inflammatory drug (NSAID) with antipyretic and analgesic activity. In recommended doses, there is no evidence that it changes a horse's innate ability to race, except to make a horse perform more nearly normal with pain due to inflammation of part of the musculoskeletal system" (Gabel et al., 1977).

It was also the opinion of many veterinarians, at that time, that PBZ would allow a horse to compete with mild chronic arthritic changes, but did not possess sufficient analgesic activity to allow a horse with a serious injury to compete. The NSAIDs can be used to restore normal performance in a horse affected by some minor injury to joints, tendons, or muscle by providing relief of inflammatory pain. Some consider the use of NSAIDs justified in jumpers, and exceptions are made in racing by some jurisdictions. Many veterinarians agreed that the use of anti-inflammatory drugs could mask unsoundness in horses being examined in a prepurchase examination for soundness (Sanford, 1983).

Results from performance studies suggested that PBZ had no clear effect on the performance of normal, healthy horses (Sanford, 1974). This impression was confirmed by exercise studies performed in the equine. Plasma concentration of prostaglandins are increased in man (Demers et aI., 1981) and equine during exercise (Birks et aI., 1991; Mitten et aI., 1995). These exercise-induced increases in cyclooxygenase activity was inhibited by the administration of PBZ, but PBZ did not produce detectable changes in systemic hemodynamic or acid-base variables in either standing or running horses (Hinchcliff et al., 1994). In a exercising horses the effect of inhibition of cyclooxygenase activity on the hemodynamic response was examined. Administration of PBZ abolished the exertion-induced increases in plasma 6-ketoprostaglandin F_{1} alpha and thromboxane B2. Phenylbutazone treatment resulted in significantly higher heart rates and right atrial pressures than control.

There was no effect of PBZ on carotid or pulmonary arterial pressures, oxygen consumption, carbon dioxide production, blood lactate concentrations, or plasma volume during exertion. These results suggest that cyclooxygenase products likely mediate or modulate some of the systemic hemodynamic responses to exertion in horses (Mitten et aI., 1996), but there is no evidence that the administration of PBZ and/or the suppression of cyclooxygenase products alters performance.

Based on these opinions and observations, investigators conducted a number of studies to determine the plasma PBZ concentrations 24 hours following various dosing schedules, formulations, and dosages (Soma et al., 1983; Chay et al., 1984; Houston et al., 1985; Soma et al., 1985). Following completion of these studies the recommended dosing schedule was as follows: oral administration of 4.4 mg/kg (2 g) for 3 - 4 days followed by a single IV dose of 4.4mg/kg 24 h prior to racing. If these dosing recommendations are followed, plasma PBZ concentrations on race day should not exceed 5 µg/ml. However, these studies did not attempt to determine the pharmacological effect of PBZ at 5 µg/ml. or the contribution by its pharmacologically-active metabolite, oxyphenbutazone (OPB).

The initial regulatory race day plasma concentrations suggested to all Commissions was 2 µg/ml., This conservative concentration was based on the opinion of many analysts that the higher concentrations of PBZ were associated with masking or interfering with drug testing in urine (Gabel et al., 1977). This was subsequently reviewed and it was concluded that this concentration could be increased to 5 µg/mL which is the regulatory limit now accepted by most jurisdictions in the United States (see footnote in reference section).

Effects of Phenylbutazone on nociception (pain perception).

Pain is difficult to assess in the horse as it is influenced by many factors. Equally difficult to assess is the alteration of pain by analgesic drugs. The latency to onset of movement of a limb in response to a noxious thermal stimulus has been used as a nociceptive end-point for analgesic studies in many species (Kamerling et al., 1985). Thermal-evoked skin-twitch reflex and thermal evoked hoof withdrawal reflex have been used to compare analgesic activity of procaine, mepivicaine and phenylbutazone. Compared to procaine and mepivicaine, phenylbutazone failed to alter pain thresholds over a 36 hours post-administration period (Kimmerling et al., 1985). This type of stimulation produces an acute pain response and can be used to objectively compare the duration of anesthetic agents regionally administered and other drugs used to reduce the perception of pain. In the horse as in other species, PBZ is not an effective analgesic drug when used to block thermal pain and specific nociceptive pain stimuli.

Central nervous system effects and crossing the 'blood brain barrier'.

Phenylbutazone has no known spinal or central nervous system effects that are involved in the suppression of pain. The effects are primarily thought to be peripheral in action with no central nervous system action or any noticeable sedation. To exert a central effect, NSAIDs have to cross the blood brain barrier

(BBB) and numerous studies have shown that they do cross the BBB (Bannwarth et al., 1989). The presence of NSAIDs in the brain may explain the antipyretic properties and some side effects of the NSAIDs. Concentrations of oxyphenbutazone (OPB) in spinal fluid are similar to corresponding concentrations of unbound free OPB in plasma, which is approximately 5% of the total concentration of OPB in plasma (Gaucher et al., 1983a). Similarly, cerebral spinal fluid concentrations of ketoprofen reflect the unbound plasma ketoprofen concentrations and were in equilibrium with the plasma concentration from 2 to 13 hours after administration (Netter et al., 1985). Ibuprofen, flurbiprofen, and indomethacin rapidly cross the BBB. Plasma protein binding limits the driving force for uptake of NSAIDs into the brain by reducing the free fraction of NSAIDs in plasma (Parepally et al., 2006). The observation that long-term treatment of patients with ibuprofen results in a reduced risk and delayed onset of Alzheimer's disease suggests that it crosses the BBB, has a central effect, and reduces inflammation in the Alzheimer's diseased brain (Dokmeci and Dokmeci, 2004). Attempts to correlate the CFS concentrations of indomethacin with its regional inflammatory suppression and analgesic activity have not been successful (Bannwarth et al., 1989). The statement that the NSAID do not have central effects and all actions are peripheral in nature is certainly not substantiated by a number of studies.

Synovial fluid concentrations of NSAIDs

There is no barrier to the diffusion of NSAIDs into or out of the joint cavity and the efficacy of INSAIDs in rheumatic diseases may depend on their concentrations within the joint. Piroxicam concentrations in plasma and synovial fluid after a single oral dose of 20 mg, in humans were 2.51 and 1.31µg/ml, respectively. The elimination from synovial fluid was longer than from plasma (Bannwart et al., 2001). Concentration of OPB in synovial fluid were 57.1% of the corresponding plasma concentration. The OPB concentration was higher in patients with severe inflammation than in those with no or little inflammation (Gaucher et al., 1983a). Concentrations of diclofenac and the diffusion of aspirin and its metabolites through the synovial membrane have also been reported (Gaucher et al., 1983b; Bannwarth et al., 1985). In horses with no joint disease, equilibrium between synovial fluid and plasma concentrations was attained in 8 hours following the IV administration of naproxen; this was followed by a parallel decline in plasma and synovial fluid concentrations for up to 36 hours (Soma et al., 1995). In the horse, ketoprofen was no longer detectable in synovial fluid after 5 h whereas synovial fluid carprofen concentrations did not peak until 12 h and were still detectable at 48 h (Armstrong et al., 1999).

Many authors have suggested that the plasma concentrations of NSAIDs do not correlate well with assessments of therapeutic response. This may reflect weaknesses in experimental design, capability of determining the changes in pain levels and inflammation, and in clinical studies the variability in the diseases being studied. It may be that concentrations in plasma bear only a distant relationship to those in the inflamed tissues where NSAID presumably act (Famaey, 1985; Grennan et aI., 1985; Simkin, 1988). Compared to the

CNS, NSAIDs readily penetrate into the joint and the concentration is not limited to the unbound fraction. The concentrations reported have been lower than in plasma. The peak concentrations and elimination from the joint are related to the pharmacokinetics and characteristics of the drug, dose and route of administration.

Post-operative pain and phenylbutazone

Post-operative pain can be considered primarily nociceptive pain produced by trauma to tissues by direct intervention and disruption of these tissues. Inflammation is a part of the pain response due to surgical intervention and the use of NSAIDs has been promoted for this purpose post-operatively. Minimal differences were noted between PBZ and placebo administrations in a group of horses undergoing arthroscopic surgery (Raekallio et aI., 1997).

In a similar post-operative study, flunixin, phenylbutazone or carprofen were administered intra-operatively just prior to the end of anesthesia. The time following surgery when additional analgesic drugs were required post-operatively were; 8.4 hours, 11.7 hours and 12.8 hours for the PBZ, carprofen, and flunixin, respectively. Horses receiving the opioid, butorphanol, during surgery needed significantly fewer analgesic agents post-operatively (Johnson et aI., 1993).

In a double-blind, randomized, prospective study of human patients undergoing arthroscopic surgery, those receiving a prostaglandin inhibitor (naproxen sodium) had significantly less pain, less synovitis, less effusion and faster recovery (Ogilvie-Harris et al., 1985; Rasmussen et al., 1993) than those without. In equally as large a prospective study, no advantages were observed over control group of patients when compared to physical therapy and administration of the NSAID, diclofenac (Birch et al., 1993).

Effects of Phenylbutazone on naturally occurring osteoarthritis.

In a randomized controlled clinical trial, efficacy and safety of paste formulations of firocoxib (Equioxx'") and PBZ in horses with naturally occurring osteoarthritis were compared. Horses were treated with firocoxib (0.1 mg/kg, orally every 24 h) or phenylbutazone (4.4 mg/kg, orally every 24 h) for 14 days. Clinical improvement was defined as a reduction of at least 1 lameness score grade or a combined reduction of at least 3 points in scores for pain during manipulation or palpation, joint swelling, joint circumference, and range of motion. Results suggested some greater improvement in some categories tested following firocoxib, but overall clinical efficacy of firocoxib and PBZ in horses were comparable (Doucet et al., 2008).

Horses with naturally occurring forelimb and hind limb lameness were exercised on a treadmill and the degree of lameness evaluated by the use of kinematic analysis while horses were trotting on the treadmill. Horses entered into the study were judged to have AAEP lameness scores of 1 to 3 based on a scale of upper severity score of 5. In a cross-over study, PBZ paste was administered at 2.2 mg/kg (orally every 12 h for 5 days), alone or in combination with flunixin meglumine administered at 1.1 mg/kg, (IV every 12 h for 5 days). Lameness evaluations were performed before and 12 hours after administration of two NSAID treatment

regimens. Administration of a combination of the two NSAIDs alleviated lameness more effectively than did oral administration of phenylbutazone alone. Base on the authors' conclusion when evaluating all 28 horses, there was a significant clinical improvement after the administration of both drugs in all horses except 5 with forelimb lameness. PBZ alone did not result in significant clinical improvement in all horses. This study suggested that the use of combinations of NSAIDs (stacking) did have a better effect at 12 hours and would have a greater effect at 24 hours and the "stacking of drugs" should be a real concern. (Keegan et al., 2008).

The analgesic effects of phenylbutazone in 9 horses with chronic forelimb lameness were studied. The horses were administered saline control or PBZ at doses of 4.4 and 8.8 mg/kg IV daily for 4 days. Peak vertical force (force plate) was measured and AAEP clinical lameness scores were assigned before initiation of each treatment. All horses were evaluated 6, 12, and 24 hours after the final dose. The vertical force was significantly increased at all post-treatment evaluation times after PBZ compared to control horses. Clinical lameness scores were significantly decreased 6 and 12 hours at both doses but were only significantly decreased 24 hours after treatment with the higher dose (Hu et al., 2005).

Force plate analysis and the AAEP lameness scoring system were used to evaluate the analgesic efficacies of flunixin (1.1 mg/kg), PBZ (4.4 mg/kg), or physiologic saline solution administered IV in 12 horses with navicular syndrome. Medications were administered once daily for 4 days with a 14-day washout period between treatments. At 6, 12, and 24 hours after the fourth treatment, AAEP lameness evaluations and force plate data indicated significant improvement in lameness from baseline values in horses treated with flunixin or phenylbutazone, compared with saline controls. The effect of flunixin or phenylbutazone was maintained for at least 24 hours but no differences from control were noted at 30 hours. Flunixin meglumine and PBZ appear to have similar analgesic effects in horses with navicular syndrome (Erkert et al., 2005).

The analgesic effects of the nonsteroidal anti-inflammatory drugs, ketoprofen at 2.2 and 3.63 mg/kg and PBZ at 4.4 mg/kg were compared in 7 horses with bilateral forelimb chronic laminitis. Hoof pain was quantified objectively by means of an electronic hoof tester and lameness was subjectively graded on a modified Obel scale. Ketoprofen administered at a dose of 3.63 mg/kg (equimolar to a dose of 4.4 mg/kg of phenylbutazone) reduced hoof pain and lameness score to a greater extent than the 2.2 mg/kg dose of ketoprofen or the 4.4 mg/kg dose of PBZ. These data suggested that ketoprofen, at the dose of 3.63 mg/kg, was more potent than phenylbutazone in alleviating chronic pain and lameness in horses. PBZ and both doses of ketoprofen were still effective at 24 h (Owens et al., 1995).

Effects of phenylbutazone on an induced lameness model.

The objective was to test the hypothesis that PBZ alleviates lameness in an adjustable heart bar shoe model of equine foot pain following a single IV dose of 4.4 mg/kg. Heart rate and lameness score (1-5) were assessed every 20 min for 2 h and then hourly through 9 h. A lameness grade of 4 was produced for the study

and no lameness was observed following the study when the set screw was removed. In the PBZ-treated horses the lameness score was lowest between 4-5 h post-treatment when the score was reduced from 4 to 1.5 compared to control horses. PBZ was efficacious in alleviating lameness in this model. The PBZ plasma concentrations were approximately 15 and 7 µg/ml at 4 and 8 hours, respectively. The study period did not include observations beyond 9 hours, but the lameness score had not recovered to baseline values at that time (Foreman et al., 2008).

Indirect assessment of duration of NSAID effects

Vane in 1971 suggested that the mechanism of the action of aspirin-like compounds was a direct inhibition of prostaglandin synthetase, thereby preventing prostaglandin biosynthesis (Vane, 1971; Moncada et al., 1974; Moncada et al., 1975; Vane and Botting, 1987).

The NSAIDs are potent inhibitor of the conversion of arachidonic acid to arachidonic acid-derived mediators of inflammation. The NSAID's site of action is the cyclooxygenase pathway, therefore, blocking the synthesis and release of prostacyclin, tbromboxane, PGE_2, and PGF_2. All NSAIDs have similar modes of action accounting for both their therapeutic and toxic effects (Lees and Higgins, 1985). There have been considerable advances in the development of pharmacodynamic/pharmacokinetic models in veterinary and human medicine and investigators are studying the effects of the drug and concurrent changes in plasma or tissue concentrations of inflammatory mediators. Modem PK/PD studies link the effect(s) of the drug to its corresponding concentration in plasma. Pharmacokinetic (PK) studies determine the effects of the horse on the drug whereas pharmacodynamic (PD) studies determine the effects of the drug on the horse. (Lees, 2004; Lees et al., 2004a; Lees et al., 2004b; Toutain and Lees, 2004). General PD/PK models have been developed for describing drug actions on various active metabolites and hormones (Krzyzanski and Jusko, 2001; Puchalski et al., 2001).

A number of studies have used the reduction in the metabolic products of inflammation as indirect models of the actions of PBZ and other NSAIDs at the molecular level on the degree and duration of action. Three types of models have been used:

1. Suppression of the release of inflammatory mediators in clotted blood samples. A number of PK/PD models have been developed using this technique (Lees et al., 1987a; Soma et al., 1992; Lees et al., 2004b; Lees et al., 2004c).
2. Suppression of the release of inflammatory mediators in tissue cage and sponge models in which a sterile carrageenan solution is injected into the cage or sterile carrageenin-soaked polyester sponge strips are inserted subcutaneously. Both are based on the creation of a mild, reproducible and reversible inflammatory reaction that causes minimal distress to the experimental animals. The acute inflammatory exudates have been shown to contain proteins, white blood cells, and eicosanoids all as a

result of the inflammatory reaction (Higgins and Lees, 1984; Lees and Higgins, 1984; Higgins et al., 1987a; Lees et al., I 987b).

3. More recently, models in humans have used flow through methods to harvest inflammatory exudates. In-vivo human bioassay can be used to study human volunteers and patients. Samples are collected from pertinent tissue sites such as the skin via aseptically inserted micro dialysis catheters. These experiments measured inflammatory substances in interstitial fluid collected from non-inflamed and experimentally inflamed skin (Angst et al., 2008a; Angst et al., 2008b).

Indirect Plasma Models

This study involved the inhibitory actions of NSAIDs on TXB_2 following a single dose of flunixin (1.1 mg/kg) or PBZ (4.4 mg/kg) to determine the duration of action of these drugs. Flunixin and PBZ produced similar degrees of reversible inhibition ofTXB_2 at 4 (98% and 88%), 8 (77% and76 %), and 24 (63 and 50 %) hours, respectively. At 48 hours, inhibition ofTXB_2 was no longer apparent (Lees et al., 1987a).

In a similar study the concurrent administration of flunixin meglumine (1.1 mg/kg, IV) and PBZ (2.2 mg/kg, IV) on the pharmacokinetics of each drug indicated that the pharmacokinetic variables calculated for each drug when administered alone and in combination were similar. Serum TXB_2 production was significantly suppressed for 8, 12, and 24 hours after administration of flunixin and phenylbutazone in combination. When these drugs were administered alone, the TXB_2 concentrations were not significantly different from control values at 24 h. Note in this study that the dose of PBZ was 2.2 mg/kg. (Semrad et al., 1993).

Indirect Tissne Models.

Distribution of PBZ and its active metabolite OPB into tissue fluids was studied by measuring concentrations in plasma, tissue-cage fluid, peritoneal fluid and acute inflammatory exudate harvested from a polyester sponge model of inflammation in ponies. PBZ and OPB readily penetrated into inflammatory sites. After six hours, the concentration of PBZ was higher in exudate than in plasma and remained so at 24 hours. Mean concentrations of OPB in all fluids were lower than those of PBZ at all times, but OPB readily entered body fluids, especially into inflammatory exudate; suggesting that OPB may contribute to the anti-inflammatory effect. The estimated elimination half-life of PBZ from exudate was 24 h compared to 5 h from plasma. These authors suggested that the persistence of PBZ and OPB in tissues exudates extended the duration of PBZ effectiveness (Lees et aI., 1986).

Other studies have shown that flunixin was also cleared more slowly from equine tissue inflammatory exudate than from plasma (Higgins et al., 1987b).

Acute inflammation was induced in 7 ponies by subcutaneous implantation of sterile carrageenin-soaked polyester sponge strips. Treatment comprised a single therapeutic dose of 4.4 mg/kg of PBZ administered intravenously at the time of sponge implantation. Exudates were harvested at 6, 12 and 24 hours and examined

for leukocyte and erythrocyte numbers. Leukocyte numbers were significantly increased from 6-hour values at 12 and 24 hours in both control and PBZ-treated animals but differences between control and treated ponies were not significant. The administration of PBZ produced highly significant reductions in exudate concentrations of PGE_2 and 6-keto-PGF ıά 6 hours. Significant reductions in these eicosanoid concentrations were maintained in treated animals for 12 and 24 hours. Concentrations of TXB_2 were reduced in treated animals at 6 and 12 hours but these changes were not significant. Study results suggested an effect at 24 hours based on the two measured eicosanoids, PGE_2 and 6-keto-PGF_1ά (Higgins et al., 1984).

In a 12-day treatment schedule, 5 ponies were administered an oral paste formulation of PBZ and 5 matched ponies were given equivalent doses of a placebo paste. On day 12, a mild, non-immune inflammatory reaction was induced subcutaneously. Exudate was collected at 4,8, 12, and 24 hours. There were no significant differences in exudate protein concentration and leukocyte numbers between the treatment groups, but exudate concentrations of 6-ketoF 1 ά were reduced at 4, 8, and 12 hours and those of TXB_2 at 8, 12, and 24 h in the PBZ treatment group. The increases in surface skin temperature were significantly less in PBZ-treated than in placebo-treated ponies between 4 and 24 hours (Lees and Higgins, 1986).

Leucocyte and erythrocyte accumulation in exudate were not affected in any of the tissue cage and exudate studies. The hypothesis of prostaglandin synthetase inhibition is the most widely accepted mode of action for the NSAIDs, but other actions of NSAIDs including leukocyte migration, neutrophil aggregation, lysosomal enzyme release, and superoxide radical generation have been demonstrated. In-vitro studies have shown that flunixin, PBZ, OPB, and indomethacin suppress leukocyte migration. Flunixin was the most potent of the 4 drugs studied (Dawson et aI., 1987).

Conclusions

This review presented an historical prospective and examined the information presented in 4 different models used to determine the effects of NSAIDs, especially PBZ. They included naturally occurring lameness, reversible induced lameness, and indirect plasma and tissue models studying the suppression of the release of arachidonic-derived mediators of inflammation. The majority of studies suggest an effect of PBZ at 24 hours at a dose of 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not examine a horse for a pre-purchase lameness examination unless the horse is shown to be free of NSAIDs and glucocorticoids. This remains the opinion of many Commission Veterinarians in that they wish to examine a horse pre-race without the possibility of a NSAID or corticosteroid interfering with the examination and masking a possible musclo-skeletal condition. Based on scientific reports and the impression of clinical veterinarians, residual effects of PBZ remain at 24 hours. The impact of this sustained effect on the health and welfare of the horse remains problematic.

Possible Approaches and Suggested Future Options.

1. The regulatory concentration of 5µg/ml should not be changed.
2. Acquire more information on the impact of residual affects of PBZ.

   Gathering of more information on the possible impact of the residual effect of PBZ and OPB on the potential for further injury would be difficult based on the number of variables that can contribute to injuries whether catastrophic or minor in nature. One of the major confounding variables is the use of intra-articular and intravenous glucocorticoids close to race day which may have a greater impact on the pre-race examination than the NSAIDs.
3. The glucocorticoids should be regulated prior to any consideration of changes in the regulatory concentrations of the NSAID allowed on race day.
4. The allowable plasma concentration of PBZ on race day could be lowered to 2µg/ml, which was the original recommendation. The 5 µg/ml plasma concentration allows greater room for flexibility in the administration of PBZ. Phenylbutazone can be administered inside the 24 hour period and still remain lower that the 5 µg/ml plasma concentration. The 2 µg/ml may allow less flexibility within the 24 hour time period and may require that the final dose administered IV be 2.2 not 4.4 mg/kg.
5. Subsequent to additional studies in a population of horses, a 48 hour regulatory plasma concentration could be established.

Footnote: Memo to Dr Robert Gowen, October 21, 1991 from Tom Tobin; Short overview on phenylbutazone and its regulations.

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There appears to be three major issues that need to be considered when evaluating the current problems facing the racing industry. Breeding, track surfaces and medication are on everyone's agenda of issues that must be addressed if our sport is to survive, much less prosper. We can no longer sit ideally by and assume that public perception is not reality. Breeding for the auction market rather than for soundness, buying for speed rather than longevity and medicating up to race time to alleviate problems brought on by this rationale has our industry on a downward spiral that must be reversed. Was it the breeder of the unsound horse or the veterinarian who tried to keep the horse racing sound with the use of medication? I can't answer the chicken or the egg question but I do feel that the first and easiest solution is to address the medication.

Changes in breeding and research on the optimum track surface will take years to accomplish the desired end result. Medication can be changed overnight. I practiced on the race track for over thirty years and have administered much more than my share of anabolic, non-steroidal and corticosteroid medications. I practiced before permissive medication and have seen controlled medication reach the point of uncontrolled. Horses are racing today on more medication than any time in the past and are having shorter careers, higher vet bills and more dissatisfied owners.

Illegal drugs are not the problem, it's the so called legal therapeutic medications that are over used and abused. Our allowable levels of therapeutic medications on race day make it extremely difficult to determine the health and soundness of the animal when a pre-race exam is conducted. Inflamed joints, muscles and mild lameness are masked by medication and therefore undetectable to the examining veterinarian. These problems may be minor until the horse leaves the starting gate but become major by the time they reach the turn for home and down the stretch, putting both horse and rider at risk.

We keep many horses racing under the influence of medication that should be retired prior to their career ending injuries. How can the breeder judge the potential of a sire or dam when performance was influenced with medication?

How does track surface research factor in medication? Having raced with so called therapeutic medication for some thirty years, I now believe we have developed a culture and a breed that is medication dependent. Anabolics need a forty five day withdrawal. Intra-articular injections should not be made within 10 -14 days minimum prior to racing and non-steroidal and corticosteroids should not be administered within a minimum of 48-72 hours prior to racing. More time and research is needed to resolve the bleeder issue but other medication issues can be changed overnight. If the veterinary profession were to endorse these changes, we would give the breeder and the track superintendant a purer model upon which to base their decision. Also, the veterinary profession would be looked upon as part of the solution and not part of the problem.

I do not believe for one minute that medication abuse contributed to the tragic death of Eight Belles but I do know that it is a problem in racing and the only one that can be changed immediately. We must do everything possible to protect the rider, the welfare of the horse and the integrity of the sport.

Tom V. David, DVM
Equine Medical Director
Louisiana State Racing Commission

EXHIBIT 3

RMTC

Racing Medication & **Testing Consortium**

Striving to develop and promote uniform rules, **policies and testing standards at the national level; coordinate research and educational** programs that seek to ensure the integrity of racing and the health and welfare **of racehorses and participants: and protect the interests of the** racing public.

Press Releases

RMTC Recommends New Phenylbutazone Threshold Level, Announces Launch of Recent Rulings ..• *4/15/10*
RMTC
NEWS RELEASE

April 15, 2010

Contact: Hallie Lewis (859) 224-2848

RMTC RECOMMENDS NEW PHENYLBUTAZONE THRESHOLD LEVEL, ANNOUNCES LAUNCH OF RECENT RULINGS DATABASE

Based on the recommendation of its Scientific Advisory Committee. the Racing Medication and Testing Consortium (RMTC) board of directors has revised its recommended threshold for the non-steroidal anti-inflammatory drug {NSAID} phenylbutazone from 5 micrograms per milliliter to 2 micrograms per milliliter of plasma or serum. Under the current model rule, one of three approved NSAIDs is permitted at least 24 hours prior to racing. The permitted NSAIDs are phenylbutazone, flunixin and ketoprofen.

"This action was taken in response to concerns expressed by the regulatory veterinary community regarding the effects of NSAID administration on pre-race examinations: said Dr. Rick Arthur, chair of the RMTC Scientific Advisory Committee and equine medical director for the California Horse Racing Board (CHRB). "The committee felt that the regulatory veterinarians' concerns that NSAID levels may compromise pre-race examinations were justified. This adjustment in permitted phenylbutazone level is measured and appropriate.'" The Scientific Advisory Committee will continue to research whether further restrictions on NSAID use are warranted.

The board made this recommendation at its meeting in Lexington Ky., on April 12, 2010, held in conjunction with the Association of Racing Commissioners International 2010 Annual Conference.

Dr. Tom David, equine medical director for the Louisiana State Racing Commission. applauded the RMTC board's action.

"We are very pleased with this step and appreciate the RMTC's willingness to address the concerns of the regulatory veterinarians," said Dr. David. 'We look forward to a continuing dialogue on the subject."

Also during the board meeting, RMTC Director of Communications Hallie Lewis announced the creation of a Recent Rulings Database to go live immediately on rmtcnet.com.

"I am excited about this project because I believe it fulfills a need in the industry," said RMTC Executive Director Dr. Scot Waterman. 'Members of HANA (Horseplayers Association of North America), racing fans and participants have voiced their desire for transparency and easy-to-access data on drug-related rulings. To our knowledge, this is the only database in existence that allows viewers to see not only the infractions but also a description of the possible uses and effects of the drug in the horse. We hope that this will begin the process of better clarifying the difference between medication management mistakes and more serious drug violations.'

Dr. Rick Sams of the University of Florida Racing Laboratory presented an update on RMTC-funded research to determine thresholds and withdrawal times for 13 medications often used *by* practicing veterinarians to treat horses in race training. This research is being conducted at the University of Florida, University of Pennsylvania New Bolton Center, Pennsylvania Equine Toxicology and Research Laboratory, Iowa State University and the University of California-Davis.

"My colleagues and I expect to publish withdrawal time recommendations on acepromazine, boldenone. butorphanol, detomidine, firocoxib, fluphenazme, testosterone, nandrolone, stanozolol and glycopyrrolate in the next 90 to 120 days," Dr. Sams told RMTC board members.

Dr. Waterman announced that negotiations are close to completion to begin the External Quality Assurance Program through an independent third-party provider. Once initiated, the program will provide proficiency, masked and double-masked urine and blood samples for participating testing laboratories to analyze for the presence and quantity of prohibited and regulated drugs.

According to Dr. Waterman, "This is the first step in implementing the RMTC Drug Testing Initiative. We expect to have a full external quality assurance program up and running in 2011."

In the interim, the Testing Integrity Program Inc. and the Interstate Drug Testing Alliance will continue their single- and double-masked sample programs with RMTC subsidization.

Dr. Scott Stanley, director of the University of California-Davis Kenneth L. Maddy Laboratory, presented a report on the CHRB frozen sample and retrospective testing program for growth hormone. This program, based on methods published by LCH, the

French racing laboratory, retrospectively tested 2,000 samples that have been frozen over the past two years under the 'CHRB's drug testing program. The growth hormone analysis of the CHRB's frozen sample program was made possible by funds provided by The Jockey Club.

In other RMTC business:

• A strategic plan was adopted that outlines research, reorganization and regulatory communications as key areas of focus in the organization's future.

• An update was given on the current research strategies involving the intra-articular administration of corticosteroids.

• An update on the efforts toward international harmonization or racing medications was given, including the steps undertaken to exchange research data.

• RMTC will create a committee to confront regulation issues and encourage uniformity across racing jurisdictions regarding policy language on out-of-competition testing.

• Current RMTC officers Dr. Scot Waterman, Dr. Robert Lewis, Alan Foreman, Chris Scherf. Dr. Rick Arthur and Tom Charters were re-elected to serve another term.

• It was announced that RMTC CEO Dan Fick has stepped down to focus on his new position as a steward tor the Indiana Racing Commission.

"On behalf of the board of directors, I would like to give a heartfelt thank-you to Dan for his tireless efforts to move this organization forward over the last several years. His commitment and dedication were truly remarkable and we wish him the best in his future endeavors," said RMTC Chairman Dr. Robert Lewis.

The RMTC consists of 25 racing industry stakeholders and organizations that represent Thoroughbred, Standardbred, American Quarter Horse and Arabian racing. The organization works to develop and promote uniform rules, policies and testing standards at the national level; coordinate research and educational programs that seek to ensure the integrity of racing and the health and welfare of racehorses and participants; and protect the interests of the racing public.

For additional information, visit the RMTC website at rmtcnet.com or contact Hallie Lewis, RMTC director of communications, at (859) 224-2848.

Exhibit 4

On September 14th the *ARCI Regulatory Veterinarian Committee* met by conference call to discuss a number of equine health and welfare issues. The racing regulatory veterinarians reiterated their concern that the permissive non-steroidal anti-inflammatory (NSAID) policies in the United States are compromising the examining veterinarian's ability to indentify horses at risk for catastrophic injury. The examining veterinarians are concemed NSAID levels at the time of the pre-race inspections mask the clinical signs of inflammation and pain. Current NSAID policies in racing regulate blood levels of these drugs at race time, not at the time of the examination. Pre-race examinations are often performed many hours before post time. Non-steroidal anti-inflammatory drugs are prohibited by International Federation of Horseracing Authorities; these drugs are not allowed at any level in most international racing jurisdictions. The *ARCI Racing Regulatory Veterinarian Committee* has called for a reevaluation of current NSAID policies in the US and a change in NSAID regulations changed to better protect the horse.

A similar issue involves the use of glucocorticosteroid (cortisone) drugs in race horses. The *ARCI RegUlatory Veterinarian Committee* is calling for a prohibition of the practice of intra-articular (joint) injections of cortisone and similar drugs within 5-7 days of racing. Cortlsones are very potent drugs used to reduce inflammation. When properly and judiciously used cortisones can be very useful in managing equine lameness. However, clinical experience has shown the examining veterinarians these drugs can be terribly misused in racehorses. While reducing inflammation can be beneficial in the short term, the underlying pathological condition is often left unchanged. If the true extent of the injury cannot be evaluated by the examining veterinarian at the time of the pre-race examination, horse and rider may be placed at undue risk. The *ARCI Racing Regulatory Veterinarian Committee* is calling for the racing industry to develop regulations and policies to restrict intra-articular cortisone injections prior to racing to better protect
horse and rider.

Phenylbutazone kinetics and metabolite concentrations in the horse after five days of administration

L. R. Soma, VMD; D. E. Gallis, BS; W. L. Davis, BA; T. A. Cochran, MS; C. *B. Woodward, PhD*

SUMMARY

Phenylbutazone (PBZ) was administered (8.8 mg/kg of body weight) every 24 hours for 5 consecutive days, orally for the first 4 days and IV on day 5. The half-life (t½) after this daily administration was 6.2 hours and the volume of distribution was 0.152 ± 0.014 L/kg; the bioavailability after oral administration was 91.8 ± 2.5%. The plasma concentration of PBZ at experimental hour (EH) 24 (24 hours after the 1st oral dose) was 1.7 ± 0.39 µg/ml and increased to 4.2 ± 0.29 µg/ml at EH 48 (24 hours after the 2nd oral dose). Values at EH 72, 96, and 120 (24 hours after administration of oral doses 3 and 4, and IV dose 5, respectively) were 4.8 ± 0.62 µg/ml, 5.3 ± 0.84 µ.g/ml, and 4.3 ± 1.1 µ/ml, respectively. Significant increases ($P < 0.05$) were measured between EH 24 and 48 with no changes during the subsequent 3 days. Changes in the urinary concentrations of PBZ were not seen over the 5day dosing period. There were increases in the metabolites oxyphenbutazone and the a-alcohol during the 5-day dosing period. There was a delay in the appearance of a-alcohol in urine after oral and IV administration.

Phenylbutazone (4-butyl-1,2-diphenyl-3,5 pyrazolidinedione, PBZ) is a nonsteroidal anti-inflammatory drug with antipyretic and analgesic activity. In the horse, it has been used for treatment of bone and joint inflammation, laminitis, and soft tissue inflammation. [1-2] The mechanism of the analgesic action is mediated by the inhibition of prostaglandin synthetase."!'

Two metabolites of PBZ in horses are oxyphenbutazone (O.PBZ), [4-butyl-1-4-hydroxyphenyl-2 phenyl-3, 5 pyrazolidinedioneJ and a-alcohol (OH.PBZ), [4-(3-hydroxy)-butyl-2-phenyl-3, 5-pyrazolidinedione].[12], [13]

The plasma half-life (t½) of PBZ in the horse is from 3.8 hours to 7.9 hours.[13-17] There is considerable variation in t½ among species, ranging from 2.9 hours in rats to a high of 77 hours in human beings.[18-23]

Daily administration of PBZ in the horse has been reported to increase the t½ or to have no effect.[24] Chronic administration Of PBZ in human beings has shown plasma values increase in a nonlinear fashion, but marked changes in plasma concentrations were not observed with a high daily dose.[25] With cessation of chronic therapy, difference in $t_{1/2}$ was not found[26]. Other studies in human beings indicated a decrease in $t_{1/2}$ after 5 days of administration.[27] In one study, twice daily oral administration of PBZ for 17 days did not affect the $t_{1/2}$.[22] The majority of the studies in human beings indicated that the $t_{1/2}$ was variable and unchanged with time and dose.[22,28]

The purpose of the present report was to describe urinary and plasma concentrations of PBZ and its metabolites during 5 days of administration, the relationship of the metabolites to the parent compound, and PBZ kinetics after 5 days of administration.

Materials and Methods

Animals and experimental design-Four healthy female Standardbred and 2 Thoroughbred horses weighing 481.1 to 583.4 kg (529.9 ± 14.3) were used. Females were chosen because of the ease of urine collection. The horses were clinically normal, had not been given any drugs within 20 days, were housed in stalls 48 hours before the study, and were given hay, oats, and water. Hemoglobin (13.6 ± 0.36 g/dl), pcv (41.5 :!: 0.85%), total protein (6.4 :!: 0.15 g/dl), and WBC counts (8,507 ± 637 cells/ml) were all within normal ranges before and after the study.

Phenylbutazone" at a dosage level of 8.8 mg/kg of body weight was administered orally via a stomach tube at experimental hours (EH) 0, 24, 48, and 72 and IV at EH 96. The mean dose was 4.67 ± 0.13 *g/day.* Blood and urine samples were collected at EH 24, 48, 72, and 96 just before the administration of the next dose and at EH 120. Sequential blood and urine samples were collected at EH 73, 74, 76, 80, 88, and 92 (1, 2, 4, 8, 16, and 20 hours after oral administration at EH 72, and at EH 97,98, 100, 104, 112, and 116 (1, 2, 4, 8, 16, and 20 hours after IV administration at EH 96). Kinetic analysis was completed on the samples collected after IV administration. Blood samples were collected in heparinized vacuum tubes and were centrifuged within 1 hour. All samples were stored at - 20 C.

PBZ analyses-Analyses of PBZ, O·PBZ, and OH·PBZ were done by gas chromatography (cc), using flame ionizing" and nitrogen-phosphorus detectors' and high-pressure liquid chromatography (HPLC) with uv light detection (Spectra-physics 8000).Gas chromatography peaks were integrated manually using peak heights, and HPLC peaks were integrated using an on-board integrator (Spectra-physics M Integrator).[d] A 0.9-mm long 2-mm internal diameter column containing 3% SP 2100 on Supelco-

Received for publication Apr 12. 1982.

From the University or Pennsylvania, School or Veterinary Medicine !Soma. New Bolton Center Campus, Kennett Square, PA 19348, and the Pennsylvania Race Horse Testing Laboratory IGallis, Davis, Cochran, Woodward), West Chester State College, West Chester. PA 19380.

Supported by the Pennsylvania Slate Horse Racing Commission and Slate Harness Racing Commission.

The authors thank Dr. Charles Ramberg for assistance in analyses or kinetic data.

• Jensen-Salsbery, Kansas City, Mo.
[b] Perkin-Elmer Corp, Norwalk, Conn. , Kontes, Vineland, NJ.
, Speclra·physics, Piscalaway, NJ.

port 100 to 120· mesh support was used for GC. The HPLC was performed with a 10 urn C," reverse phase column (4.6 mm ID x 25 cm long).

Plasma and urine (5 ml each) were used for extraction for GC nitrogen-phosphorus detection and HPLC, and 10 ml of urine was used for GC analysis with flame ionizing detection. The appropriate volumes of plasma or urine were added to 2 ml of saturated KH.PO. and 2 ml of CH.CL." mixed for 5 minutes, and centrifuged. The CH,CL,. fluid (l ml) was transferred to capped tubes, and 1 µl was injected for GC analysis. The extraction procedure for liquid chromatography differed in that 5 ml of CH.CL. was used. All the CH.CL, extract was dryed under N. and dissolved in 1 ml of methanol, and 10 µl was injected. Pure PBZ and O·PBZ[r] were used for standards, added to plasma and urine, and extracted in a similar manner. Standards for OHPBZ were purified from equine urine samples, using thin-layer chromatography. Three separate extractions were done, and each extraction was analyzed in triplicate.

Oven temperature for GC was 210 C, and the carrier gas was N, with flow rates of 30 to 40 *ml/min.* The nitrogen-phosphorus detector was operated in the nitrogen mode. The HPLC was run isocratically with a solvent composed of a 40:60 mixture of acetonitrile and 5 x 10 - ·*M* solution of L-heptane sodium sulfonate" at 2 ml/min and 40 C with detection at 220 nm.'9 All extraction and chromatographic solvents were pesticide or HPLC grade, according to the operations being performed.

Pharmacokinetics and data analyses-Data for each horse were evaluated by examination of semilogarithmic plots of the plasma concentration-time curves. This indicated that the data fit a l-compartment open model. A linear regression was used to determine overall elimination rate constant (β). Because 1st samples were collected 1 hour after oral or IV administration of the drug, the initial distribution phase was not measured, and plasma data were handled as a 1-compartment model. The $t_{½}$ of the drug was calculated from 1n 2/β.

The apparent volume of distribution (V_d) was estimated from the area under the IV plasma concentration curve (AUC) as:

$$V_d = \text{Dose}/\beta \cdot \text{AUC}$$

The specific volume of distribution (V'.) is the V_d expressed in kilograms of body weight. The AUC of the f-compartment model was calculated by integration of the plasma decay curve. The plasma drug concentration immediately after the IV injection (C~) was determined by extrapolation to time zero. The bioavailability (F) of the oral preparation was determined by:

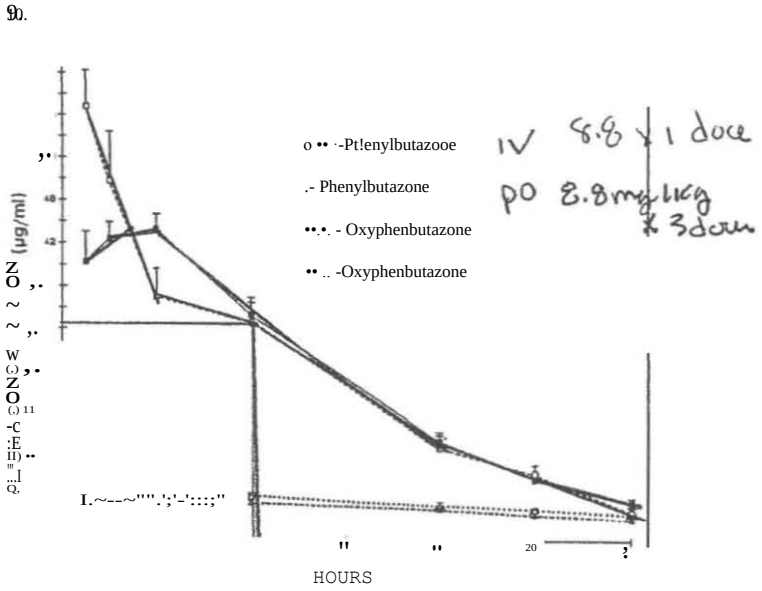
$$F = (\text{AUC, oral})/(\text{AUC, IV}) \times 100.$$

Total body clearance (CL_a) was calculated from estimates of V_d, x β.

All data were expressed as the arithmetic mean ± SEM. The harmonic mean was used for the $t_{½}$ because $t_{½}$ are reciprocal values." The Duncan multiple range test for van able responses was used for the analysis of sequential data. Linear regression was the least squares method, and the Student's *t* test was used to compare the means of 2 independent samples. Differences were considered significant at a probability of < 0.05.

Results

Plasma concentrations-Plasma concentrations of PBZ collected at EH 24, 48, 72, and 96 (24 hours after oral doses 1, 2.3, and 4 of 8.8 mg/kg of PBZ. respectively) were 1.7 ± 0.39,4.2 ± 0.29,4.8 ± 0.62, and 5.3 :t 0.84 •.•. g/ml, respectively. The plasma PBZ concentration at EH 120 (24 hours after IV administration) was 4.3 ± 1.1 •.•. g/ml. There was a significant difference ($P < 0.05$) between concentrations at EH 24 and concentrations at EH 48, 72, 96, and 120, but there were no differences in plasma concentrations between EH 48, 72, 96, and 120.



Rg 1-Plasma concentration of PBZ and O·PBZ during a 24-hour period after oral administration (closed symbols) and IV administration (open symbols). The oral dose of 8.8 *mg/kg* was given at EH 72 and the IV at EH 96. Mean ± SEM of 6 horses.

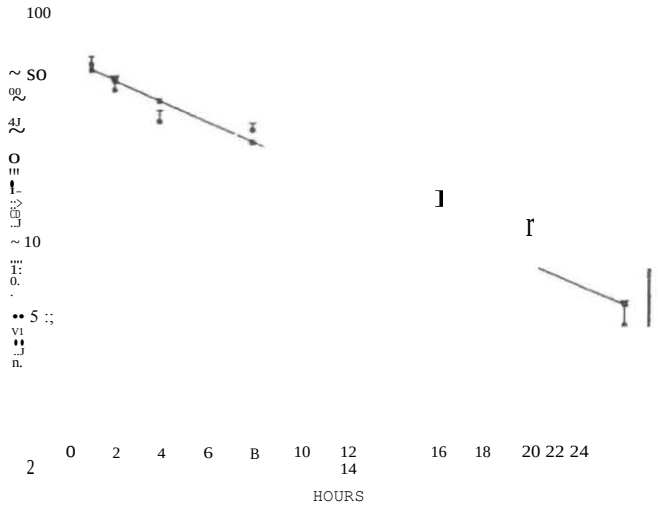


Fig 2-Log base 10 plot of plasma PBZ after IV administration of 8.8 mg/kg at EH 96 .• = the regression of all data points .• = mean :t SEM 01 6 horses.

At EH 73 (1 hour after oral administration of dose 4), the mean plasma PEZ was 39.4 :t 4.4 µg/ml, and reached a plateau at EH 74 and 76 with concentrations of 42.5 ± 2.3 and 43.8 ±2.1 µg/ml, respectively. The difference among these 3 values were not significant. The bioavailability after oral administration was calculated as 91.8 ± 2.5%. At EH 97 (l hour after the IV dose), the mean plasma PBZ was 61.1 ± 3.5 µg/rnl (Fig 1). Pharmacokinetics after the IV injection were described by a L-compartment open model (Fig 2; Table 1).

• Supeleo Co, Belfort, Pa.
r Geigy Pharmaceuticals, Ardsley. NY . •
Aldrich Chemical Co, Meluchin, NJ.

TABLE 1 Kinetic values after the administration of PBZ (B.B mglkg)

Horse No.	II'" Ihr-I	13 rhr II	V'. IUk!:1	Cl_{II} Iml/minlkl(l	C_{r}	"U"·IV I~glhr/mll	Alll'·oral IILg/hr/ml	F I'kl
I	IUO	0.114	0.134	0.254	62.7	605	58\	96
2	**6.73**	**0.103**	**0.J08**	**0.185**	79.9	835	683	82
3	*fi.52*	0.126	0.209	0,437	49.9	406	404	100
4	6.60	0.105	0.136	0.239	60.7	67\	60\	90
S	6.93	0.100	0.\51	0.195	66.6	789	708	90
6	*fi,42*	0.128	0.\74	0.370	54.3	436	407	93
Harmonic mean ± SEM	6.\6	O.113~, 0.00-';	0.152:!: 0.014	0.280:= 0.041	62,4 :!:	623.7 :!: 72.4	564,8 :!: 53.8	91.8 :!: S.S

TABLE 2-Urinary concentrations of PBZ and metaboliles after consecutive administrations

	PU7.	D-I'IIi'.	nu.rnz
1':11	IILg/mli	1~I':!mll	l~g/mll
24	4.B ::: 1.2	22.9:!: 0.5	5.\ :!: 0.9
48	~.9 :!: 0.66	*fi9.5* :!: 12.8'	12.4 :!: 2.9'
i2	1i.9 :!: 0.44	*i8.6* :!: t3 . .1*	\2.9 :!: 1.8*
96	4.B :!: 1.0	9B.1 :!: 18.7*	37.5 :!: 5.9",f
120	4.0 ~ 0,96	84.8 :!: 18.0'	29.0 :!: 3.6*,+

'i **SiKnificRnl** difference **from Foil 24** concentrations, t Significant **difference** from Ell 48 and 72 concentration s.

Data expressed **as mean -:- SF-M for 6** horses.

Plasma O-PBZ concentrations increased progressively after daily oral administration from 0.93 ± 0.16 µg/ml at EH 24 to 1.9 ± 0.23, 2.1 ± 0.29, and 3.1 ± 0.49 *µg/ml* at EH 48, 72, and 96, respectively. The 120-hour concentration was 3.6 ± 0.46 µg/ml (24 hours after IV administration at EH 96). There was a significant difference among plasma values at EH 24 as compared with those at EH 48, 72, 96, and 120 and values at EH 48 and 72 when compared with that at EH 120. The highest plasma O-PBZ measured was at the 8-hour period after oral (EH 72) and IV (EH 96) administration (Fig 1l. The 8-hour plasma concentrations after oral and IV administration were signif-icantly different (P < 0.05>.

The plasma OH-PBZ values were low, ranging from 0 to 2 *µg/ml.* Plasma OH·PBZ values of 1 µg/ml were determined 1 hour after oral (EH 72) and IV (EH 96) administration of PBZ. There were no measurable amounts at EH 24, 48, and 72 and concentrations at EH 96 and 120 < 1.0 µg/ml.

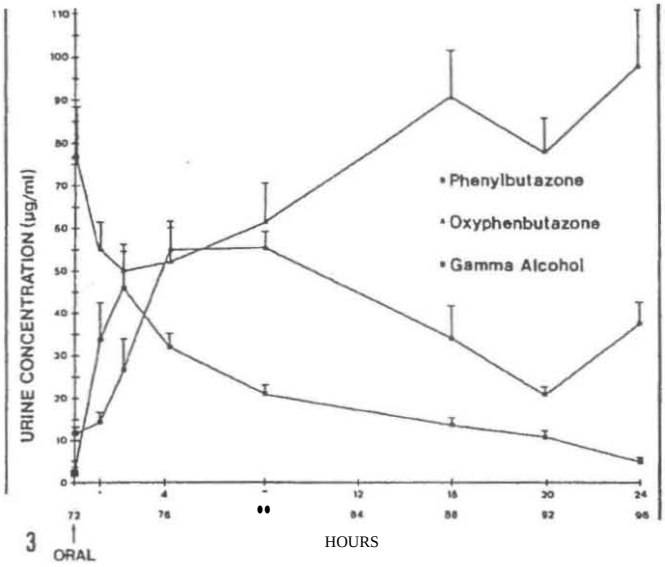


Fig 3-Urinary concentrations of PBZ (-), O·PBZ (A), and OH·PBZ (e) after oral administration of 8.8 mg/kg at EH 72. Concentrations indicated at EH 72 are urinary concentrations just before oral administration. Urinary PBZ concentrations peaked at 2 hours. There was a rapid decline in urinary O.PBZ concentrations as urinary PBZ concentrations increased. This was followed by an increase in urinary o-opz as the urinary PBZ values Increased. The t-hour urinary OH·PBZ did not differ significantly from the EH 72 values, began to increase at 2 hours, and peaked at 4 hours.

Urinary concentrations-Urinary PBZ increased slightly at Ell 72; however, there were no differences in the urinary concentrations over the 5-day dosing period (Table 2\. At [~H 74 (2 hours after oral administration at EH 72). the urinary PBZ peaked and the mean concentration was 46.2 ::: 9.0 I-lg/ml (Fig 3l. At EH 97 (I hour after IV administration of PBZ at ~~H 96), urinary PBZ was 56.7 ::: 9.25 *1l-f{/ml* (Fig 4). The rapid decline of PBZ in the urine paralleled changes in the plasma concentrations for oral and IV administration. There was an excellent correlation between the decrease in urinary and plasma concentrations after oral *(R* = 0.95. *P* < 0.01) and IV (R = 0.99, *P* < 0.01) administration.

The concentration of urinary O·PBZ decreased as the urinary PBZ values increased after oral and IV administration (Fig 3, 4, and 5l. As the values of urinary PBZ gradually decreased. there was a subsequent increase in the values of urinary O·PBZ. The correlation between the urinary PBZ and the urinary O·PBZ changes was *R* = -0.95, *P* < 0.02 for the changes after oral administration and *R* = - 0.99, *P* < 0.01 for the relationship after IV administration. .

There was a significant increase *(P* < 0.05) in the trough values of urinary O·PBZ when comparing that' at EH 24 with that at EH 48 (Table 2). There were considerable variations in the concentrations of urinary O-PBZ at EH 24, 48, 72, 96, and 120, but these concentrations were not significantly different, with the exception of the value at EH 24.

The trough concentrations of urinary OH·PBZ metabolite did not follow the pattern noticed with urinary PBZ and urinary O-PBZ (Table 2). At EH 48 and 72, urinary concentrations were significantly higher than that at EH *24 (P* < 0.05), and those at EH 96 and 120 were significantly different from those at EH 48 and 72 *(P* < 0.05).

At EH 73 and 97 (l hour after the oral and IV PBZ at EH 72 and 96), urine values of OH·PBZ had not increased (Fig 3 and 4). Values increased at 2 hours and peaked at 4 hours (Fig 3 and 4). There was a slower decline in the urinary OH-PBZ (Fig 3) after oral administration than there was after IV administration (Fig 4). The 4-hour (EH 100) urinary OH-PBZ concentrations were high after IV administration which was followed by a rapid decline at EH 104.

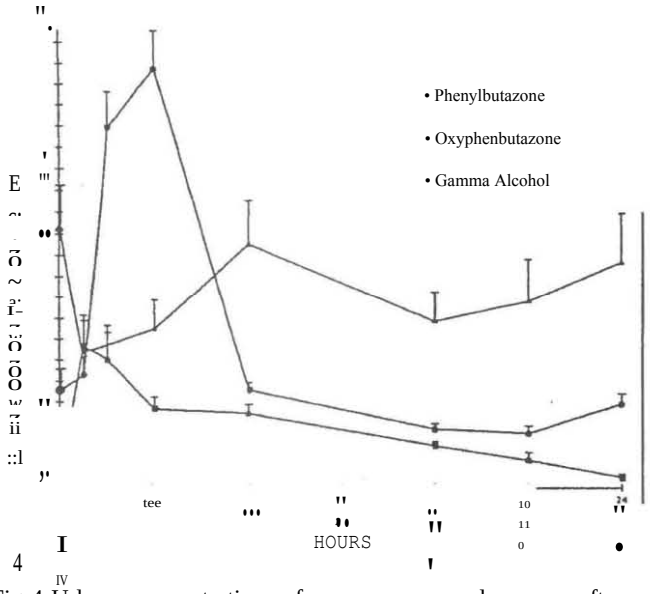


Fig 4-Urlnary concentrations of PBZ (.). O·PBZ (A), and OH·PBZ (e) after IV administration of 8.8 mg/kg on EH 96. The concentrations indicated at 96 hours are the urinary concentrations before the IV administration. The urinary PBZ peaked at 1 hour, and as with the oral dose, the urinary O·PBZ values declined sharply as the urinary O-PBZ values increased. The urinary OH·PBZ values increased sharply at the 2-hour period and peaked at 4 hours. The urinary OH·PBZ concentrations were high for the first 8 hours after IV administration.

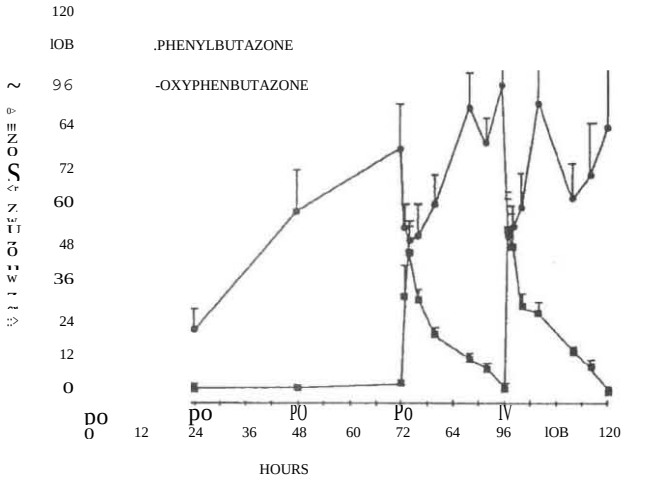


Fig 5- The relationship of the urinary concentration of PBZ (.) and o-pbz (e) during the 5·day dosing period. Mean ± SEM for 6 horses. PO = per os.

The value at EH 104 was the same as those at EH 96 and 120. After both administrations, the urinary OH-PBZ values were lower than the O-PBZ values after 8 hours.

Ratios of urinary PBZ/OH-PBZ at the EH 24, 48, 72, 96, and 120 were 0.16 ± 0.06,0.09 ± 0.03,0.09 ± 0.02,0.05 ± 0.01, and 0.06 ± 0.01. The lower ratios at EH 48, 72, 96, and 120 reflect the higher concentration of urinary 0PBZ in the face of steady trough concentrations of urinary PBZ during this 5-day dosing period. In comparing the ratios at the 24-hour postadministration periods, significant differences were found between values at EH 24 and 48 (Fig 61.

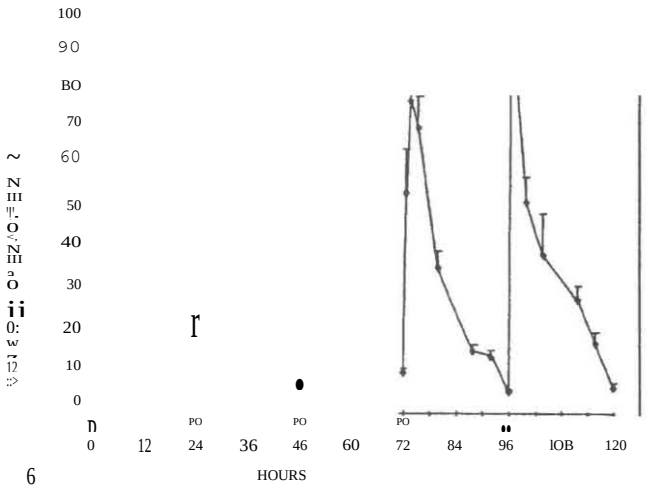


Fig 6--Urine ratios of PBZO·PBZ concentrations for the 5-day dosing period. Mean ± SEM for 6 horses.

After oral administration of PBZ at EH 72, the urinary ratio of PBZ/O-PBZ increased from 0.09 at EH 72 to 0.55, 0.90, and 0.67 at EH 73. 74. and 76, respectively (Fig 61. This reflects the rapid urinary excretion of PBZ with actual decreases of urinary O-PBZ as this occurs (Fig 5). The decrease in the ratio is marked from 8H 104 through 96 (8 to 24 hours after administration) as the O·PBZ in urine increases and the concentrations of urinary PBZ decrease. The ratios at the 1-, 2-, and 4-hour periods after administration were not significantly different. Differences became significant when comparing the 4-hour plateau with the 8 through 24 hour plateau *(P* < 0.05).

After IV administration, the ratio at EH 97 was> 1 reflecting a rapid excretion of PEZ from plasma into urine and a reduction in urinary O-PBZ. Compared with that after the oral administration, the peak ratio declined more rapidly during EH 97 to 104 (l to 8 hours after administration); the urinary PBZ rapidly declined. Values at EH 104, 112, 116, and 120 were significantly different from each other *(P* > 0.051.

Discussion

The t½, for PBZ in 6 horses was 6.2 hours after 8.8 mg/kg orally at EH 0, 24, 48, and 72 and IV at EH 96. This falls within the ranges reported by others and is similar to the t½ for a single administration of 6.0 mg/kg. [17] This similarity was despite 4 days of oral administration before the TV dose. The plasma data after IV administration were fitted to a l-cornpartment model, because the 1st samples were collected at hour 1 (EH 97); therefore, missing the initial distribution phase. Phenylbutazone plasma decline has also been described as a 2-compartment model. [17]

The possibility that daily administration increases the *t½,* in the horse has been suggested, because slight increases were noticed after 4 days. [13.] Increases reported appeared to be within the normal variation expected. In the present study, the 95% confidence limits bracketed a t½, from 5.64 to 6.79 hours. A single injection study indicated a similar variation." Kinetic studies in 4 horses

indicated no significant differences in the $t_{1/2}$ after 13 days of oral treatment. [24] Recent studies in human beings are similar, in which no change in $t_{1/2}$ was found after chronic administration or increasing doses of drugs.[22] This is despite a slow rate of metabolism in human beings. The 24hour trough plasma concentrations of PBZ were consistent after the first 24 hours with little accumulation of PBZ and no differences in plasma concentrations were noticed at EH 48, 72, 96, and 120. The urinary concentrations of PBZ showed no significant change over the 5-day dosing period. Five days of administration does not represent a long-term chronic administration of the drug, but no changes in trough concentration during the 5-day period indicate a rapid attainment of a steady state situation, and the elimination of the drug can be predicted, even after daily use.

The rapid renal excretion of PBZ in the horse, compared with that in other species, is partially related to the negative logarithm of the dissociation constant (PK_a) of the drug in relationship to the alkaline pH of horse urine. This inverse relationship of the PK_a. to the rate of elimination has been studied in dogs and human beings.[20,31] The more acid analogues of PBZ (PK_a = 2.3 to 3.1) studied in other species were excreted more rapidly than were analogues with a high PK_a (4.5 to 5.5). The tubular epithelium is permeable only to the more lipid soluble nonionized component of the drug molecule; therefore, minimizing back diffusion and enhancing its elimination. The alkaline urine in the horse favors this effect, but cannot account totally for the rapid elimination of the drug in the horse. In the horse, metabolites account for the major percentage of drug recovered in the urine.[13] An increasing concentration of urinary OB-PBZ at EH 96 and 120 indicated an increase in the output of this metabolite as administration of PBZ continued. Increase in plasma concentrations of OH-PBZ have been reported in human beings during chronic administration.[32]

Metabolites of PBZ are less lipid-soluble, the partition coefficient between peanut oil and saline buffer at pH 7.4 is 2.2 for PBZ and 0.6 for O·PBZ and OH·PBZ. The PK_a of these 3 compounds are 4.5, 4.7, and 4.0, respectively." This decrease in solubility of the metabolic products and more rapid excretion of the metabolite when compared with that of the parent compound is predictable." This decreased solubility increases renal excretion by limiting back diffusion by the distal tubules. The metabolites are also less protein-bound; therefore, increasing glomerular filtration." The degree of plasma binding in the horse is 96% for PBZ and 87% for O.PBZ, [15] as compared with 99% and 94% in human beings, respectively. [21] Plasma binding for OH·PBZ has been reported as 85% in the dog.[21] This can partially account for the rapid renal appearance of PBZ in the urine of the horse. Mutual displacement of PBZ and O·PBZ from serum albumin has been reported with the higher concentration of one drug replacing the other at binding sites.[32]

There was a sharp decline of urinary O·PBZ after the oral and IV administration of PBZ (Fig 3 and 4). This decrease in urinary O·PBZ was more marked after IV administration than after oral administration (Fig 5). This decline paralleled the increase in urinary PBZ.

The decrease in O·PBZ urine values as the urine values of PBZ increase may be related to direct competition with PBZ due to the high plasma values. Renal studies in human beings indicate that the concentration of PBZ in the tubules is in excess of the quantities filtered by the glomerulus. The high plasma binding limits the amount filtered; this indicates an active secretion in the proximal tubules, enhanced by higher plasma values." Phenylbutazone is one of the acid drugs that are excreted in the proximal portion of the renal tubules by a carrier-mediated transport system. [32] Reducing the elimination of its own metabolite, especially during high plasma concentrations of the parent drug, is a possible explanation for the reduced concentrations of urinary O-PBZ at peak concentrations of urinary PBZ. There is an increase in the plasma concentration of O·PBZ during the reduction of the urinary O.PBZ, maximizing at 8 hours followed by a decrease (Fig 1).

The rapid, but delayed, increase in the urine concentration of the OH-PBZ starting at the 2nd hour and peaking at the 4th hour after administration is unexplained. This is followed by a rapid decrease.

The delayed appearance of the OH-PBZ in urine indicates a delay in the conversion of OH·PBZ from PBZ or 0-PBZ or a delay in its release into plasma. The specific metabolic pathways of these 2 metabolites have not been delineated.

After IV administration, the urinary OH-PBZ was consistently higher than the urinary O·PBZ values at the 2-and 4-hour periods and lower than the urinary O-PBZ between 8 and 24 hours (Fig 4). After oral administration, the urinary OH·PBZ was lower than the O·PBZ with the exception of the 4-hour period (Fig 3). The O·PBZ urinary concentrations are higher after the oral administration as compared with that after the IV administration.

The relationship between PBZ and its metabolite O-PBZ reflected the change in the relative concentrations of both between EH 24 and 48. The EH 24 ratio is the highest base on lower urinary O·PBZ when compared with that at EH 48, 72, 96, and 120.

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EXHIBIT 6

Prairie Meadows Historic Catastrophic Breakdown Statistics
2000·2011

	STARTERS	BREAKDOWNS	FSI·INDEX
2000	8,382	11	1.31
2001	8,452	11	1.30
2002	8,417	5	.59
2003	6,181	7	1.1.3
2004	5,951	14	2.35
2005	6,997	5	.71
2006	5,562	10	1.80
2007 **	6,494	11	1.69
2008	7,122	13	1.83
2009	6,470	16	2.47
2010	6,593	13	1.97
2011	6,322	13	2.05

*FSI Index is Catastrophic Events/l000 starts.

** 2007 Allowed Phenylbutazone plasma level raised from 2.2 micrograms/ml to 5.0 micrograms/ml.

2010/2011 Had separate Thoroughbred and Quarter Horse meets. The separate data is available for those years. The previous years had a Thoroughbred meet followed by a mixed meet in the fall.

EXHIBIT 7

10/25/2010

RCI Lowers Bute Threshold

Lexington, Ky. - In an effort to improve the pre-race examinations of racehorse, the Board of Directors of the Association of Racing Commissioners International (RQ) gave final approval today to lower the allowable level of phenylbutazone

The board voted 16-0 in favor of lowering the threshold for penalty from 5 micrograms of phenylbutazone (bute) per milliliter of plasma or serum to 2 micrograms, paving the way to improved pre-race examinations conducted by regulatory veterinarians.

RO President Ed Martin said "Absent a compelling and convincing medical reason to the contrary, the RCI has concluded that it is in the interest of the horse that the proposed change be adopted: He noted that RCI will now review the current penalty guidelines to address concerns that have been raised pertaining to potential first-time violations of the new rule. RCI's Model Rules Committee, in supporting the change, recommended that Jurisdictions work with local horseman's groups to transition to the new policy and consider a grace period so trainers can adjust.

The change to the Model Rule comes after months of research and discussion, beginning with the RCI Regulatory Veterinarian Committee, who voiced concerns that phenylbutazone could Interfere with pre-race examinations due to the possibility of analgesic effects of the drug. RCI asked the Racing and Medication Testing Consortium (RMTC) to review the research on the topic, and the Scientific Advisory Committee of the RMTC voted without objection to support the lowering of the threshold.

The RCI Model Rules Committee had planned to vote on the matter during a spring meeting, but at the request of the National Horsemen's Benevolent and Protective Association (HBPA) delayed that vote until after the topic could be discussed at their Annual Meeting.

After considering alternate viewpoints expressed at the National HBPA meeting, the RCI Model Rules Committee voted in favor of lowering the threshold in September. The lowered threshold received formal support from groups such as the American

Association of Equine Practitioners, The Jockey Dub, The Jockeys' Guild, and the Thoroughbred Owners and Breeders Association,

Because the proposed new racing regulatory compact is not yet in existence, the adoption of the model rule change will occur In different Jurisdictions at different times, as individual commissions commence formal rule making on an individual basis.

In related news, the RCI Board of Directors voted 11-1 (4 abstentions) in favor of a change to the Model Rules dealing with fees paid to jockeys of Thoroughbred, Quarter Horse, and other flat races. The new rule clarifies when jockey fees are earned by riders, and specifically deals with situations when changes are made to the rider of a horse by an owner, trainer, or tile jockey.

Putting the Horse First:

Veterinary Recommendations for the Safety and Welfare of the Thoroughbred Racehorse

American Association of Equine Practitioners
4075 Iron Works Parkway Lexington, KY 40511
(859) 233-0147 • www.aaep.org

The American Association of Equine Practitioners was founded in 1954 by 11 racetrack veterinarians. While the association has grown to serve nearly 10,000 members worldwide who work with all equine breeds and disciplines, the AAEP's horse racing origin brings a unique understanding of the health and welfare needs of the racehorse.

It is with this perspective and commitment to equine safety and welfare that the AAEP formed its Racing Task Force in July 2008 to evaluate the safety and welfare issues affecting Thoroughbred horse racing. Catastrophic injuries, medication usage and a changing societal view of the appropriate use of horses in competition present formidable challenges to those entrusted with the care of the racehorse and the structure of the industry.

The AAEP Racing Task Force developed this white paper with the intent of recommending practices that place the welfare and safety of the horse first while supporting those who seek to make meaningful change. As equine veterinarians, we are committed to working with the Thoroughbred racing industry to implement procedures that protect the horse. In addition, the AAEP expects its veterinary members to abide by the rules of all jurisdictions where they practice.

General Principles

The AAEP has long held position statements that address many aspects of racehorse health and safety. We encourage the Thoroughbred racing industry to support the following essential elements of an overall industry structure that promotes horse safety:

- The adoption of uniform rules of medication usage, testing, security and enforcement by all industry participants.
- Increased funding for regulatory functions, including state-of-the-art testing and racetrack security.
- Continued identification and implementation of procedures and strategies that will significantly reduce the injury rate of horses, such as the recent recommendations to eliminate the use of toe grabs other than wear plates with a height no greater than 2 millimeters.

The AAEP makes the following recommendations for the Thoroughbred racing industry in four key areas: societal change and the public perception of horse racing, the racing business model, the veterinarian-owner-trainer relationship, and medication.

Societal Change and the Public Perception of Racing

Since the tum of the century, American society has drifted far from its agrarian roots to the point that only 15 percent of Americans today are involved with agriculture of any form. The horse, which was once a staple of American agriculture and general transportation, has become less of a beast of burden and is now viewed by many in the

public to be a companion animal, much the same as a dog or cat. In this societal context, welfare issues affecting the horse resonate with the public like never before.

In order to address the impact of societal change upon the Thoroughbred racing industry, the AAEP recommends:

- Racing industry support for a strategic plan that places the safety and welfare of the horse among its highest priorities. It is imperative that the industry urgently demonstrate an ability to affect sweeping change without government intervention. The AAEP recognizes and supports efforts by the National Thoroughbred Racing Association (NTRA) to accomplish this goal.
- The continued collaboration of multiple racing organizations (NTRA, TOBA, HBPA, ARCI, The Jockey Club, AAEP, racetracks and sales companies and others) to address the challenges affecting racing. An excellent opportunity for a cooperative industry-wide effort is the NTRA Safety and Integrity Alliance, and the AAEP enthusiastically supports this effort.
- When the substantive issues of race horse welfare have been addressed by the industry, an aggressive public relations effort must be mounted to educate the public about what is being done to protect the welfare and safety of the horse (e.g.: racetrack injury reporting program, racetrack surface testing and medication studies).

The Business Model of Racing

Thoroughbred racing is a $15 billion industry in the United States, and the business model has evolved over the years to favor training and racing of two- year-old horses that compete for championship purses late in their two-year-old year. Their peak earning potential is in the three-year-old year, with a gradually diminishing emphasis on continued racing into the four-year-old year and later.

Thoroughbred racing operates on a year-round schedule in 38 separate racing jurisdictions. Because a larger field of horses promotes more wagering, which in turn increases purse size, small field sizes have caused racing secretaries in some instances to apply pressure to trainers to enter horses who might not otherwise be suitable for racing. This practice must be eliminated, as it encourages entry of horses at shorter intervals that may place them at increased risk of injury due to increased frequency of high-speed cyclic loading. Another concerning trend is an increasing number of racino executives that do not have experience in horse racing or horse care. We believe it is imperative that senior racetrack management become knowledgeable about the issues and business practices that directly affect the welfare and safety of the horses that race at their tracks.

As noted, two-year-old racing is an important aspect of the industry business model. Some degree of training and racing of two year olds is not harmful to the welfare and safety of the horse. In fact, a review of Jockey Club information indicates that horses that race as two year olds are more successful and race longer than horses that do not race at

the age of two. However, not all horses are able to sustain the same level of training without significant stress or injury. There is a need for continued investigation of the welfare and safety implications of current policies and procedures employed to sell, condition and race two-year-olds.

Other practices that will improve the safety of the racehorse include the development of a consistent protocol for pre-race examinations by regulatory veterinarians as well as uniform criteria for scratching horses. Currently there is variation in these procedures among the 38 racing jurisdictions. There also is lack of uniformity in reporting racehorse injuries, particularly those that occur during morning workouts. Judicious application of a standardized reporting system will increase the racing industry's ability to monitor and address racing and training injuries.

In most racing jurisdictions there is no institutional program to care for horses that can no longer race. The view of most racing facilities is that the responsibility for the care of horses rests entirely with the owner. This view is entirely appropriate. However, if a horse owner does not provide responsible care for retired racehorses, the industry becomes vulnerable to attack for apparent lack of concern for equine welfare. The resulting negative impact on horse racing's image can contribute to disenfranchisement of racing fans.

The AAEP acknowledges that the following recommendations for modification of the business model of racing will have significant economic implications (some positive, some negative) for racing managers. We do not make these recommendations lightly. Further, we emphasize that one of our highest priorities as an industry must be to reduce equine injuries. The greatest potential for decreasing injury exists in making procedural and policy changes within the business model of racing, particularly in the claiming arena.

In order to put the safety and welfare of the horse first in the business model of racing, the AAEP recommends:

- A critical analysis by the racing industry of the safety and welfare implications of the current schedules, procedures and policies surrounding the conditioning, sale and racing of two- year-old horses.
- A period of rest for all horses to provide an opportunity to refresh and diminish the volume of persistent cyclic loading that occurs in the absence of rest.
- No horse shall be permitted to race within 10 days of its last start.
- Every horse entered to race shall be on association grounds in sufficient time to have a pre-race veterinary inspection for racing soundness by the regulatory veterinarian.
- Standardization and enhancement of pre-race and post-race veterinary examinations with mandatory cross-jurisdictional sharing of information.
- In those jurisdictions that practice it, racetrack management must discontinue the coercion of trainers to enter horses according to stall allotment.

- Uniform participation by all jurisdictions in injury reporting for both racing and training injuries.
- Investment by all racing venues in capital improvements of the racing oval that will enhance horse, rider and personnel safety, such as safety rails, padded starting gates, and helmets and vests for starting gate personnel.
- Immediate adoption of ARCI riding crop and shoeing standards in all racing jurisdictions and at in-training sales.
- The development in all racing jurisdictions of a program for rehabilitation, retraining and adoption for horses whose racing careers have ended. These programs should reinforce owner responsibility and support a secondary market for racehorses. The Finger Lakes Thoroughbred Adoption Program in Farmington, N.Y., is an example of successful collaboration between racetrack management and horsemen. Any new programs can be linked nationally with the Unwanted Horse Coalition, currently operated by the American Horse Council.
- The generation of funds by the industry to assist in the transition of horses from racing into second careers.
- Governance change within the horse racing industry to establish uniform regulatory authority to accomplish widespread and consistent compliance throughout the industry.
- Development of continuing education and accreditation programs for owners, trainers, stewards, jockeys, grooms, starters, farriers, veterinarians and security personnel.

Claiming Races

There are essentially two groups of horses that compete at the racetrack. The sport's top level competitors, representing approximately 30 percent of the total racing population, compete in stakes and allowance races, while the majority of horses compete in condition or claiming races. Because the schedules and physical demands on these two groups of horses are unique and quite disparate, the AAEP recommends the following changes to the structure of claiming races in order to protect the welfare and safety of claiming-level horses:

- Claimed horses must be tested post-race, as is currently the rule in New York. Horses that test positive shall have the claim rescinded at the discretion of the buyer.
- No claiming race should have a purse that exceeds the claiming price by more than 50 percent.
- If a horse is claimed, it shall not start in a claiming race for a period of 30 days since the date of claim for less than 25% more than the amount for which it was claimed.
- When appropriate, horses must demonstrate a work between races that displays fitness and soundness.
- Horses that do not finish the race or those that sustain a catastrophic injury during the race remain the property of the original owner.

Veterinarian-Owner- Trainer Relationship

Open and consistent communication between the owner, the trainer and the veterinarian will develop a relationship built on trust and shared philosophies. The result will be decisions that are made in the best interest of the horse. The current reality of racetrack operations is that the owner is often excluded from the communication chain, and we as veterinarians would like to change that. Veterinarians also are sensitive to the costs of services that are provided. It is important for owners to know that veterinary care is not given to any racehorse without the trainer's direct or implicit approval and that their trainer is acting as their legal agent when requesting veterinary services for their horses. Without open communication, differing management philosophies often result in confusion and dissatisfaction.

In order to provide complete transparency for the veterinary-owner-trainer relationship, the AAEP recommends the following:

- Trainers should include horse owners in all aspects of health care decisions.
- Owners should have a thorough understanding of the medication and training philosophy of their trainer with particular emphasis upon the level of medical care provided to their horses.
- Veterinarians should provide unfettered access to owners and trainers for consultation and discussion of medical treatments.

Medication

While much progress toward uniformity has been made by industry stakeholders such as the Racing Medication and Testing Consortium in recent years, medication remains the flash point for much of the public's scrutiny of horse racing today. U.S. racing jurisdictions impose medication regulations that vary from one jurisdiction to the next. This disparity in medication rules presents significant challenges to owners and trainers who race horses in more than one jurisdiction, and often leads to confusion about how to best implement appropriate therapeutic regimens. In addition, many racing jurisdictions have their own testing laboratory, which currently do not operate by a uniform accreditation standard.

Horse racing in most other jurisdictions throughout the world operates under the medication rules of the International Federation of Horseracing Associations (IFHA). The principle difference in the medication regulations of the United States and the IFHA is the permitted use of anti-bleeder medication furosemide (Salix® and adjunctive antibleeder medications in some racing jurisdictions) and permitted levels of non-steroidal anti-inflammatory drugs (NSAIDS). With anabolic steroid regulation now in place in the United States, most other differences are largely semantic and are primarily a function of the state regulatory structure of U.S., racing.

All medication treatment programs should be based upon the safety and welfare of the horse. While the veterinarian is ultimately the provider of medical care for the horse, treatment philosophies should be determined in conjunction with input from the owner and trainer.

With regard to medication policy in the United States, the AAEP recommends the following:

~ • Universal adoption in all racing jurisdictions of the Association of Racing Commissioners International (ARC I) model rules, as proposed by the Racing Medication and Testing Consortium (RMTC), including no race-day medication except furosemide (Salix®). The industry should work with the RMTC, where advisable, to make progress toward uniform medication rules that are in the best interest of the horse.

- Continued research, with industry support, to determine the causes and appropriate treatment of exercise-induced pulmonary hemorrhage (EIPH) in the race horse.
- Collaboration between the RMTC and the IFHA to create an international model rule of racing that can be uniformly administered worldwide.
- Establishment of a limited number of regional confirmation/reference laboratories that are adequately funded to meet the current challenges of drug testing.
- Establishment of minimal requirements, accreditation and monitoring of all testing laboratories.
- Development of uniform testing protocols for accredited laboratories.
- Adoption of uniform out-of-competition testing protocols by all racing jurisdictions.
- Adoption of uniform TC02 testing protocols by all racing jurisdictions.
- Universal adoption of the penalty structures recommended in ARC I model rules and proposed by the RMTC.
- Adoption of uniform reporting practices for medication violations by all racing jurisdictions.
- Management of medication violations by racing jurisdictions with three objectives in mind: (1) to discover how the medication entered the system of the horse in order to prevent future positive tests; (2) to manage and report sub-therapeutic levels of therapeutic medication overages in a way that does not further degrade the public image of racing; and (3) to sufficiently penalize the violators and discourage further attempts to violate the rules
- The key to successful implementation of these medication recommendations is **increased racetrack security** to promote enforcement and achieve uniform compliance.

Horses Intended for Sale at Public Auction

The treatment of horses intended for sale at public auction should be regulated in a similar way as for horses that are racing. The adoption of similar regulations will protect the horse and ensure the integrity of the sales process, recognizing that the sales process is a unique experience for immature horses.

The AAEP recommends the following actions in regards to medication usage in race horses intended for sale:

- Yearling and 2-year-old in training sales should institute stringent medication rules that are similar to RMTC guidelines.
- Yearling and 2-year-old in training sales should institute random testing of horses consistent with RMTC testing protocol recommendations.
- Any health problems that require medical treatment on the sales grounds must be announced in a timely manner, giving the buyer time to consult with a veterinarian prior to purchase.
- A list of all medications administered to a horse while the horse is on the sales grounds and being displayed to potential purchasers should be submitted to the sales company. If testing results vary from this list, the sale may be voided at the buyer's discretion.
- Penalties for medication violations at auctions must be significant to deter consignors from medication practices that may place the horse at increased risk of injury and/or compromise the integrity of the sales process.

The AAEP's mission is to promote the health and welfare of the horse. Although the focus of the AAEP Racing Task Force has primarily been the Thoroughbred racing industry, nearly all of the recommendations put forth are relevant to other racing breeds in the United States. To this end the AAEP is eager to assist the racing industry in reforming policies and practices in order to enhance the safety and welfare of the horse by putting the horse first. We believe that this effort, based upon what's best for the horse, will also be the key to restoring public confidence in the racing industry. Simply put, what is good for the horse is good for racing.

Respectfully completed by the AAEP Racing Task Force:

Jay Addison, DVM
Kathleen Anderson, DVM
Rick Arthur, DVM
Don Baker, DVM
Jeff Blea, DVM
Larry Bramlage, DVM
Tom Brokken, DVM
Doug Corey, DVM
Reynolds Cowles, DVM
Tom David, DVM
Steve Dey, DVM
Chip Johnson, DVM
John Kimmel, DVM Robert
Lewis, DVM Wayne
McIlwraith, BVSc Nicholas
Meittinis, DVM John
Mitchell, DVM
Foster Northrop, DVM, Vice Chair
Gary Norwood, DVM
Scott Palmer, VMD, Chair
Gregg Scoggins, DVM
Mary Scollay, DVM

Kevin Dunlavy, DVM
Jim Gilman, DVM
Eleanor Green, DVM
Scott Hay, DVM Steve
Hurlburt, DVM Martin
Ivey, DVM

Bruce Solomon, DVM
Keith Soring, DVM
Harry Werner, VMD
Nat White, DVM
John Whittaker, DVM
Daniel A. Wilson, DVM
Bryan Young, DVM

Approved by AAEP Board of Directors, January 2009.

EXHIBIT 9

Bute, DMSO Threshold Levels to Change in Pennsylvania

SmnnPak" PhBrm'acv

Allowable level cut by 60%

The PA Horse Racing Commission made a positive stride at their most recent meeting on August 12 by mandating that *Rule 163.304 Substances of Therapeutic Value* be followed. What this means is the long-standing rule addendum of allowing 5 micgrograms per ML of Phenylbutazone (Bute) instead of the legal amount of 2 micrograms per ML has been rescinded and effective September 15, 2010. any horse over 2 micrograms will be subject to fine and/or loss of purse earnings.

The press release sent to horseman in Pennsylvania encourages them to adhere to the revised policy to avoid a positive test. This will be a significant adjustment for the backside at most tracks within the Commonwealth. Many horseman are opposed to the new rule because they believe it will preclude many horses from competing which will affect field size and create a financial strain on owners. Proponents say if a horse can't race on 2 mcg of Bute on race day that they should not be competing.

In other news, railbirds who have had to endure the pungent smell of Dimethyl Sulfoxide (DMSO) from many horses competing at Pennsylvania tracks can take a deep breath (literally) as Pennsylvania established a new threshold for the anti-inflammatory. Effective September 15, any horse who carries 10 micrograms per ML of OM SO may be subject to fine and/or loss of purse.
OM SO is often been given as a "OMSO Jug" which is injected directly into the bloodstream. This new legislation does not preclude horseman from using DMSO topically or as a sweat, but any horse administered DMSO intravenously will result in a positive drug test. OM SO is a critical medication for any horseman to have in their barn. OMSO is a tremendous at alleviating swelling and has been instrumental in treating horses with head trauma and swelling of the Central Nervous System.

Many people within the racing community have been critical of the PA Racing Commission in the past year for their handling of the Michael Gill situation as well as their failure to crack down on repeated drug positives.

- Neil Parker

Neil Parker is a *freelance contrtbutor to Business* as *Usual: Monitoring Penn National.*

Posted by Moderator at 941 PM

1990 when t was supposed to go golfing but my friend made me watch the Preakness because he had $10 on one of the horses. I was hooked. When Pennsylvania got slots I figured we would learn from the mistakes of our neighboring states about the perils of slots. Instead, we are led by a clique HBPA, a racetrack who wants to eliminate horse racing and a Racing Commission who is led by people who were appointed from the "Parks and Recreation" committee and know nothing about horse racing I When Michael Gill's horses started snapping legs off at a ridiculous rate I got angry! The problem was nobody else did. This bothered me and I truly believe that we are lead by some of the most cement headed people in the world and if that doesn't change soon we will all be watching racing on TV instead of participating in it. We have five years to fix racing in PA or we will be running for $5,000 pots once again.

View my complete profile

Current US State Regulations Pertaining to the June 2012 TRA Statement on Equine Safety

Jurisdiction	Phenylbutazone Level?
TRA GOALS	**2 mcg**
Arkansas	Graded stakes 2 meg All other races 5 meg
California	2 mcg
Delaware	2 mcg
Florida	2 mcg
Illinois	2 mcg
Iowa	5 mcg
Kentucky	As of 9-1-12: 2 mcg
Louisiana	Under review
Maryland	2 mcg
Minnesota	Under review
Nebraska	5 mcg
New Jersey	2 mcg
New York	2 mcg
Ohio	2 mcg
Oklahoma	5 mcg
Oregon	5 mcg
Pennsylvania	2 mcg
Texas	2 mcg
Virginia	2 mcg
West Virginia	Graded Stakes 2 mcg; all other races 5 mcg (2 mcg for all races in comment period)
Total 20	

EXHIBIT 11

CALIFORNIA VOTES TO REDUCE BUTE THRESHOLD

by Paulick Reoort Staff 107.21.2011 I 4:07pm

The California Horse Racing Board voted 4-3 Thursday to reduce the allowable levels of the anti-inflammatory known as Bute. The lower levels take effect January 1st, the same deadline as a policy by the American Graded Stakes Committee, which also calls for a 2 nanogram threshold for all graded stakes races.

The Breeders' Cup and Jockey's Guild favored the G'lange. The Thoroughbred Owners of California and California Thoroughbred Trainers opposed it.

PR Features

RadngFuture.com presents Photos of the Week 8.20.12

The Lane's End Weekender Pedigree: Point of Entry

Vinery LTD presents the Paulick Belmont Index: Hearts, Minds (and Bets)

The Breeders' Cup Forum: Fravel on Host Site Selection

onB Showcase: Memory Harbor (a.k.a. "Arabella")

Keeneland presents American Graded Stakes Standings: On Broken Glass, Too?

Three Chimneys presents Good News Friday: The MllJion's Investment

EXHIBIT 12

KHRC Medication and Penalty Regulation Changes for Thoroughbred racing

Please be advised that the following changes to 810 KAR 1:018 and 810 KAR 1:028 are anticipated to go into effect on September 4, 2012:

1. Phenylbutazone threshold: 2 mcg/ml serum

- The administration constraints have not changed. A maximum dose of 2 mg/lb may be administered intravenously no later than 24 hours prior to post time for the race in which the horse is entered.
- Note: The threshold and withdrawal guidance were developed based on RMTC elimination data in which the dose of PBZ was calculated based on the horse's weight. The KHRC recognizes that scales are not available, and that a weight determination is, at best, an estimate. The use of a uniform dose of 2 grams for all horses will result in risk of an overage if administered to horses weighing substantially less than 1,000 lbs. Veterinarians are encouraged to adjust dosage to the estimated weight of the animal.
- For those wishing to exercise additional caution, the administration of PBZ at 30 hours (24 hours + ½ life [6 hours]), prior to the horse's post time will eliminate any risk associated with an egregiously miscalculated dose.
- For horses having been administered repeated oral daily doses of PBZ, it is recommended to discontinue PBZ at 48 hours and use one of the other approved NSAIDs (flunixin or ketoprofen) at 24 hours.
- Please note: There is a specified route of administration (intravenous) for PBZ at the 24 hour deadline. This is consistent with the previous regulation and does not represent a change. Some trainers have indicated that they have been administering PBZ orally at 24 hours. This was, and is, a violation of the regulation. With the lowering of the PBZ threshold, oral administration establishes substantial risk of a post-race concentration > 2 mcg/ml.

2. The use of adjunct bleeder medications will be prohibited within 24 hours of a race.

3. The following thresholds and withdrawal guidelines have been adopted:

- Firocoxib 20 ng/ml serum (Veterinarians are advised to review the withdrawal guidelines provided for firocoxib)
- Methocarbamol 1 ng/ml serum
- Glycopyrrolate 1 ng/ml urine OR 3.5 pcg/ml serum

4. The following medications have been assigned penalty classifications:

Class A: Cannabinoids (synthetic), Cobratoxin, Conotoxin, Dermorphin, Inositol Trispyrophospate (ITPP), Levamisole*/Tetramisole, Methylene dioxypyrovalene (MDVP or 'Bath Salts')

Class C: Diclofenac, Firoxocib

* Levamisole has been assigned Penalty classification A in light of its documented stimulatory effect on the central nervous system. The KHRC recognizes that Levamisole has legitimate therapeutic use and does not wish to prevent horses from receiving appropriate veterinary care. Rather, the KHRC intends that Levamisole not be administered in proximity to a race. Further, the KHRC does not provide withdrawal guidance for substances associated with a Class A penalty, but does wish to inform veterinarians and horsemen that Levamisole is currently not being detected in post-race samples. To the extent that Levamisole is currently being administered, that administration would not result in a rule violation.

Individuals having questions or concerns may contact Dr. Mary Scollay at: (859) 246-2040 or mary.scollay@ky.gov
Kentucky Thoroughbred withdrawal guidelines and the Uniform Classification of Medications and Foreign Substances schedule are attached.

Attachment(s) from Mary Scollay Ward

2 of 2 File(s)

TB-QHWithdrawalGuideline-final-4-10-12.docx.dot

DrugandMedicationClassificationSchedule-final-4-10-12.rtf

EXHIBIT 13

From: "Hallie Roach Lewis" <hlewis@rmtcnet.com>
Date: Thu, 30 Aug 2012 13:31:27 -0400
To: Hallie Lewis<hlewis@rmtcnet.com>
Subject: RMTC NEWS RELEASE - STATEMENT FROM THE RACING MEDICATION AND TESTING CONSORTIUM

NEWS RELEASE

August 30, 2012
Contact: Hallie Lewis (859) 224-2848

STATEMENT FROM THE RACING MEDICATION AND TESTING CONSORTIUM

The Kentucky Horse Racing Commission recently approved regulations based on the Association of Racing Commissioners International (RCI) Model Rules. The regulations concern major medications reported to the public in racing forms. These model rules, which incorporated broad industry input, were originally developed by the RMTC.

Simply put, the model rules:

- Limit race-day medications to furosemide (Lasix), the only medication shown conclusively to reduce exercise-induced pulmonary hemorrhage (EIPH);
- Limit administration of race-day furosemide to non-practicing veterinarians to restrict access to in-today horses; and
- Reduce the threshold for the non-steroidal anti-inflammatory drug (NSAID) phenylbutazone from five micrograms per milliliter to two micrograms per milliliter of plasma or serum in post-race samples, minimizing the action of this medication during pre-race examinations.

The Kentucky HPBA recently challenged those regulations before members of the Kentucky Legislature.

According to RMTC Chairman Dr. Robert Lewis, "The RMTC-recommended model rule on race-day medication was developed by the RMTC after thorough analysis of available scientific and veterinary data. It was thoughtfully discussed and considered by all members and was approved by an overwhelming majority of the board of directors.

"Ultimately, the board determined that approving these regulations was imperative to protecting our equine athletes and furthering the RMTC's mission of strengthening the integrity of racing," said Lewis. "Furthermore, each provision was already being successfully administered at one or more racing jurisdictions in North America when they were developed as a national uniform model rule."

The regulations as approved by the RMTC were presented to and approved by the RCI. Many jurisdictions and race tracks have already successfully approved one or more of these regulations for Thoroughbred, American Quarter Horse, Standardbred and Arabian racing. The RMTC recommends that all racing jurisdictions adopt the RCI Model Rules.

"Adoption of these regulations by racing commissions is an important step for uniform rules, policies and testing standards at the national level," said RMTC Executive Director and COO Dr. Dionne Benson. "The racing public and racing participants deserve a national uniform medication policy. We encourage Kentucky and all horse racing jurisdictions in the U.S. to adopt them."

The RMTC consists of 25 racing industry stakeholders and organizations that represent Thoroughbred, Standardbred, American Quarter Horse and Arabian racing. The organization works to develop and promote uniform rules, policies and testing standards at the national level; coordinate research and educational programs that seek to ensure the integrity of racing and the health and welfare of racehorses and participants; and protect the interests of the racing public.

For additional information, visit the RMTC website at rmtcnet.com or contact Hallie Lewis, RMTC director of communications, at (859) 224-2848.

~ Bluegrass Equine
KENTUCKY DIGEST

EXHIBIT 14

theHORSE.com

CA.UKY.EDU/EQUINE | THEHORSE.COM | APRIL 2012

Exercised-Induced Inflammation and Injury in Racehorses

When 2010 Horse of the Year Zenyatta crossed the finish line for the last time, most race fans focused on the fact it was the first loss of her career. But what might be even more notable is that it was also her 20'h start-unusual in an industry that has seen an overall decline in starts (down to 6.11 per horse in 2010).

One of the reasons researchers propose for this decline is the modernday Thoroughbred's questionable durability. David Horohov, PhD, William Robert Mills Chair at the University of Kentucky's Gluck Equine Research Center, however, believes the breed is not necessarily becoming more fragile, but rather more susceptible to injury due to breeding strategies, training methods, and increased drug use. During the Veterinary Science Seminar "The Effect of Training and Nutritional Supplementation on Exercise-Induced Pro-Inflammatory Cytokine Gene Expression in 2-Year-Old Thoroughbreds," held March 20 in Lexington, Ky., he explained how we might ultimately be able to identify individuals at-risk for injury and, thus, try to prevent those racing and training injuries from occurring in the first place.

The statistics in racehorse "wastage" due to injury are shocking: Less than 60% of 2-year-olds in training race, and less than 80% of those continue to race as 3-year-olds, said Horohov. Careerending injuries are, for the most part, musculoskeletal and include bowed tendons, suspensory ligament injuries, fractures, splints, and osselots (traumatic fetlock joint arthritis), among others.

Horohov presented the theory that these injuries are often the result of mild to moderate damage occurring over time at a rate that exceeds the affected tissues' healing capabilities. He believes if researchers can develop a method to identify at-risk horses based on inflammatory response, they could prevent more injuries.

Inflammation (identifiable by swelling, pain, loss of function, and redness) occurs when tissue signals cells to respond to damage. Even a small amount of tissue damage can trigger this inflammatory response; thus, exercise itself can induce inflammation, Horohov explained. This exercise-induced tissue damage is part of the musculoskeletal healing and repair process as an individual adapts to exercise.

"While some inflammation is necessary for tissue repair, exaggerated inflammatory responses are likely associated with injury:' he said.

In his recent study, Horohov and his colleagues evaluated exercise-induced inflammation in young racehorses in training. He hypothesized that as the horses become better conditioned, their inflammatory responses will de-

Dr. Horohov's goal is to identify racehorses at risk for injury based on inflammatory response.

Articles of Interest

Inflammation and Injury

crease and they will eventually reach an anti-inflammatory state. He added a nutritional supplement (by Equine Nutraceuticals) containing antioxidants and anti-inflammatory components as topdressing to half the study horses' daily rations to determine whether it also helped reduce inflammation.

The study involved 25 2-year-old racehorses in training under one Maryland trainer. In the randomized, double-blind experiment, 12 horses received a placebo top-dressing and 13 received the supplement. All horses trained on a grass track at increasing speed and duration over an eight-week period. The researchers collected blood samples prior to exercise, immediately post-gallop, and two hours after exercise at the beginning of training and again at weeks 2, 6, 7, and 8. They then measured blood samples for lactic acid (which increases fatigue) and malondialdehyde (MDA, an indicator of oxidative damage to membranes) levels as well as pro-inflammatory cytokines (inflammatory mediators) and lyrnphokine-activated killer cell activity induced by exercise.

Upon reviewing the results, Horohov observed a time- and intensity-dependent increase in lactate immediately after exercise. "Horses are, in fact, responsive to different intensity exercise," he said. Though not statistically significant, he also observed an MDA increase. The supplement appeared to have minimal effect on the results.

The blood samples taken two hours post-exercise also showed a time- and intensity-dependent increase, this time in inflammatory cytokine expression. Horohov noted that inflammatory response was less in horses given the supplement.

"As training continued, we saw a decrease in pre-exercise inflammatory cytokines (indicating adaption to exercise)," he explained. "The most profound effect was seen in the supplemented horses."

Horohov concluded that exercise results in characteristic changes in cytokine gene expression in acute and late response. He noted that racehorse owners and trainers could potentially use this information to identify successful adaption to exercise. The supplement appeared to enhance the horses' adaptation to exercise, perhaps by reducing inflammation and oxidative damage.

Of note, Horohov said three of the 25 study horses failed to finish the study due to injury. All three completed the third exercise test and developed lameness days later, after subsequent training. These horses all showed a significant increase in cytokine levels two hours postexercise in comparison to the healthy horses. He noted that this information could be used to monitor horses in training for changes that could indicate impending injury, necessitating a break from training.

Horohov now intends to conduct another study of 100 2-year-olds in training to determine the relationship between cytokine gene expression and occurrence of specific training-related injuries. His ultimate goal is to use this technique to identify horses at risk of injury during training and on the racecourse. UK\

>Alexandra Beckstett is the associate managing editor of *TI7e Horse: Your Guide to Equine Health Care.*

Updating Equine Influenza

Equine influenza last made headlines in 2007 with the Australia epizootic that affected approximately 50,000 horses. Since eradicated from Australia, equine flu viruses still circulate in much of the world, including the United States. Antigenic drift, which produces new virus strains and gradually undermines existing vaccines' effectiveness, necessitates periodic vaccine updating to combat the new strains.

The vaccine manufacturers look to scientists to advise them on which vaccine virus strains need to be replaced and with what. In 1995 an ad hoc working group of equine flu scientists was founded for just this purpose. Called the Expert Surveillance Panel, this group includes scientists from the OlE (World Organization for Animal Health) reference laboratories for equine influenza in England, Ireland, Germany, and the United States; other labs specializing in equine flu virus; and the World Health Organization.

Scientists now recognize three surviving branches of the equine flu "family tree."

Each year the panel assembles and reviews evidence of equine flu activity worldwide, looking especially for cases of infection in vaccinated horses. It also reviews data comparing flu strains isolated from the past year's outbreaks with flu strains used in vaccines. The critical piece of evidence is how well the antibodies stimulated by vaccination will react with the circulating flu strain in the exposed horse. Researchers at Cambridge University have developed a new technique called "antigenic cartography" that makes these analyses easier. Fortunately, in most years the Expert Surveillance Panel reports that the equine flu vaccines are still working effectively. However, constant surveillance is critical.

Scientists now recognize three surviving branches of the equine flu "family tree," one of which currently circulates in the United States: the Florida clade 1 branch typified by strains such as Ohio/03. The Florida clade 2 branch constitutes the majority of recent isolates from Europe and is typified by strains such as Richmond/07. Some older American strains such as Kentucky/97 are antigenically similar to Richmond/07. The branch called the "Eurasian lineage" circulated mainly from 1990 to 2005.

Because many horses travel internationally, the Expert Surveillance Panel's latest recommendation is that equine flu vaccines should contain strains of both the clade I and clade 2 branches. The panel has stopped recommending the Eurasian branch. The original equine flu branch, the Al subtype represented by Prague/56, has apparently died out.

It is vitally important to the vaccine updating process that equine flu outbreaks are diagnosed properly and that virus specimens are collected by submitting nasal swabs from affected horses to veterinary diagnostic laboratories. From these swabs, scientists can isolate and compare

EXHIBIT 15

1.

CLOSURE OF THE DISTAL RADIAL EPIPHYSIS AND ITS RELATIONSHIP TO UNSOUNDNESS IN TWO YEAR OLD THOROUGHBREDS!

1. T.A. Mason M.V.Sc, M.R.C.V.S., M.A.C.V.Sc.[1],
2. J. M. Bourke B.V.Sc, M.A.C.V.Sc.[2]

Article first published online: 10 MAR 2008

DOl: 10.1111/j.1751-0813.1973.tb05205.x

Issue

Australian Veterinary Journal

Volume 49, Issue 5, (/doi/l0.l111/avj.1973.49.issue-5/issuetoc) pages 221-228, May 1973

Additional Information

How to Cite

Mason, T.A. and Bourke, J. M. (1973), CLOSURE OF THE DISTAL RADIAL EPIPHYSIS AND ITS RELATIONSHIP TO UNSOUNDNESS IN TWO YEAR OLD THOROUGHBREDS. Australian Veterinary Journal, 49: 221-228. doi: 1O.III1/j.1751-0813.1973.tb05205.x

Author Information

*Department of Veterinary Clinical Sciences, University of Melbourne, Werribee, Victoria, 3030.

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tPresented at the Annual General Meeting of the Australian Veterinary Association in Brisbane on 30 May, 1972.

Publication History

2. Issue published online: 10 MAR 2008
3. Article first published online: 10 MAR 2008
4. Received for publicatoin 26 May 1972.

- Abstract
- References (/doi/10.1111/j.1751-0813.1973.tb05205.x/references)
- Cited By (/doi/10.1111/j.1751-0813.1973.tb05205.x/citedby)

Get PDF (2206K) (/doi/1O.1111/j.1751-0813.1973.tb05205.x/pdf)
First page of article

ORJGI NAL ARTICLES

CLOSURE OF THE DISTAL RADIAL EPIPHYSIS AND ITS RELATIONSHIP TO UNSOUNDNESS IN TWO YEAR OLD THOROUGHBREDS*

T. A. MASON, M.V.Sc., M.R.C.V.S .• M.A.C.V.Sc.

and J. M. BOURKE, B.V.Sc., M.A.C.V.Sc.t

Introduction

The careers of many Thoroughbred racehorses are marred or terminated prematurely by unsoundness which develop when racing as two year olds, Common problems are sore-shins, carpitis. splints, sesamoiditis, sesamoid fractures and sprained joints and tendons. There appears to be no recorded information on the incidence of these conditions or of overall wastage in two year old Thoroughbreds but the results of personal observations and communications with practising veterinarians suggest that the incidence of unsoundnesses and relate these W skeletal maturity Australia. This is probably due to an increased emphasis on the racing of two vear olds because many owners desire to give their horses an early opportunity to become profitable.

In Australia many Thoroughbreds are actually racing before their second birthday at which age they are relatively immature and much of the unsoundness which develops can in general terms be attributed to immaturity, overwork, or defective conformation, or a combination of these which this epiphysis dosed either early (7 months) or late (12 months +). Studying the epiphysis of the tuber calcls, Banks *et al* (1969) gained the impression that there was a reduced incidence of lameness if horses were withheld from training until this epiphysis had closed. Other workers {Reed 1965} have used the distal radial epiphysis as an indicator of maturity but a critical evaluation of the practice has not been recorded.

Materials and Methods

General Plan

Access to 100 two year old thoroughbred was obtained through the co-operation of 15 trainers in the Melbourne Metropolitan area. The project commenced in September 1969 when the majority of the horses were In full training for the early two vear old trials and races. The group comprised 48 fillies and 52 racing colts, and 61 sires were represented, Repeated clinical and radiographic examinations were made during the racing season and records were made of all reports of unsoundness. A final examination and assessment of soundness was made at the end of the season.

At the first examination the horses' lees were

Although many of the conditions commomy encountered are amenable tO medical or surgical treatmennt, results are difficult to assess especially in terms of regaining full potential. Much effort, time and money is wasted and the prevention of unsoundness, if it is possible, would be eminently more satisfactory.

For these reasons the authors set out to study the progress of a group of two year old Thoroughbreds, to record the incidence of the various unsoundnesses and relate these to skeletal maturity as measured by radiographic closure of the distal radial epiphysis at the commencement of their racing careers.

Work on similar lines has been in progress in the USA for some time. Studying the distal epiphysis of the third metacarpal bone, Monfort (1967) recorded a higher incidence of lameness and poorer performance records in horses in

* Department of Veterinary Clinical Sciences, University of Melbourne, Werribee, Victoria, 3030.
‡ Victoria Racing Club, St Kilda Road, Melbourne, 3004.
† Presented at the Annual General Meeting of the Australian Veterinary Association in Brisbane on 30 May, 1972.

of the right fore leg In order to access the degree of closure of the epiphyseal plate. This epiphyseal plate was selected because it could be expected to close at the time of the first examination which also coincided in many horse with their first race. The degree of epiphyseal closure was thus used as a measure of skeletal maturity so that comparison could be made between horses which commenced racing with a c1osed epiphyseal and those which commenced racing with an open epiphysis.

Radiography

In each horse two radiographs of the carpus were taken. The first was in antero-posterior view with the X-ray beam centered on the epiphyseal plate. The second was an oblique view centered on the inter-carpal joint and positioned so as to visualize the antero-medical aspect of the carpal bones, for the reason that this site was prone to injury. Radiographs taken from this position are also helpful in assessing epiphyseal plate closure because the epiphyseal gap in the anterior cortex of the bone can be demonstrated clearly. It is important that the X-ray beam is horizontal and centered on the epiphyseal plate and that the cassette is held close to the leg and at right angles to the beam, otherwise severe distortion of the image of the epiphyseal plate is produced.

Daniel J. Burba, DVM, Diplomate ACVS
Professor, Equine Surgery
Equine Health Studies Program
LSU School of Veterinary Medicine

Introduction

One of the most common problems that young race horses develop is bucked shins. It has been reported that 70% of young Thoroughbred racehorses in training develop the problem. Bucked shins are commonly accepted by veterinarians, trainers and owners as a normal training event in young Thoroughbreds. Bucked shins usually occur in 2 year-old racehorses during the first six months of their training. The estimated losses to the industry as a result of the problem exceed $10 million/yr. Approximately 12% of horses that develop buck shins go on to have stress or saucer fractures later. Technology has recently allowed a better understanding of the disorder. Training appears to play a major role in its development.

What are Bucked Shins?

Bucked shins is an inflammatory condition of the front (dorsal) cortex of cannon bones. It is part of a complex called dorsal metacarpal disease. Both front legs can be affected. If both legs become involved it is of the left that develops problems first because of the counterclockwise direction of racing in the U.S. and the higher loading of the left in the turns. Bucked shins is a result of high-strain repetitive motion injury within the cannon bone. The repetitive motion injury comes from the rigorous training regimen that 2 year-olds often face and inability of the bone to adapt fast enough. As the horse becomes older the cannon bone becomes stiffer and thus rarely will bucked shins occur again.

Clinically, the condition is diagnosed by physical examination using palpation of the cannon region in which heat, pain upon pressure over the area, and swelling is detected over the dorsal or dorsomedial surface. The horse may be short-strided or lame. Radiographs may also show changes but may lag the clinical signs. Radiographic changes include new bone formation on the [periosteal] surface and thickening of the front of the cannon bone (Figure 1).

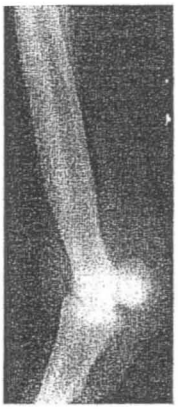

Figure 1. Radiographic appearance of bucked shins. Notice the thickening of the front of the bone.

Treatment of Bucked **Shins**

There are many different treatments for bucked shins. Pin firing and blistering are the most commonly used forms of treatment. These forms of treatment cause heating of the tissue, and the theory is that heat helps damaged tissue to heal by increasing the circulation to the area. The secret to the use of these irritants, however, is the rest that goes along with the paint. Also too much irritation causes tissue damage and is counterproductive especially if applied over the fetlock joint as well. Other treatments that are used include periosteal scraping to encourage more micro circulation to improve healing. Cold water hosing, icing, along with phenylbutazone (an anti-inflammatory) administration and stall rest is most often recommended until the pain and swelling has gone. If this course of action is not taken immediately and the horse continues to train, it may take be four to six weeks before the pain and swelling subsides. Unfortunately some horses go on to develop stress or saucer fractures in the cannon bone even up to a year after bucking their shins (Figure 2).

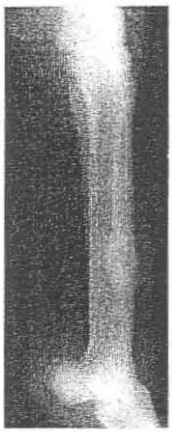

Figure 2. Radiographic appearance of a stress fracture of the cannon bone.

This is another part of the complex of dorsal metacarpal disease. Dorsal cortical stress fractures in young horses may resolve with conservative treatment as discussed above. Convalescent period may be 4 to 6 months, because fracture healing is slow in the cannon bone. Older horses that get these, which is the case most of the time, surgery is recommended. Two surgical treatments are used. Either or both may be used in a case. One technique is to place a screw across the stress fracture line to try to stabilize the fracture (Figure 3).

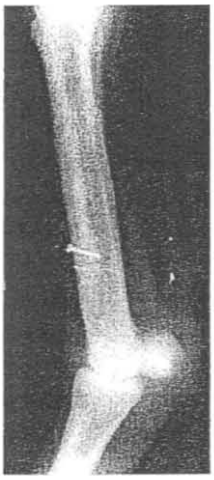

Figure 3. Insertion of a lag screw in a stress fracture of the cannon bone.

The other technique called osteostixis is to drill several small holes across the fracture line into the marrow cavity (Figure 4). This allows bone marrow cells to flow into the fracture line to enhance healing.

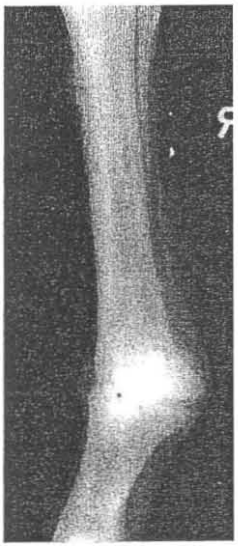

Figure 4. Drill holes placed across a stress fracture in the cannon bones.

Recently extracorporeal shockwave therapy has been used with success. The goal of these treatments is to achieve complete healing in a shorter period of time. However, convalescent time is still 6 to 8 months in most cases. It is also important that serial follow-up radiographs be taken every 30 to 45 days to assess healing.

Prevention of Bucked Shins

The type and intensity (speed) of training and racing determines what type of stresses will be placed on the cannon bone. For instance, a Thoroughbred's cannon bones remodel their structure into a different shape than a Standardbred racehorse. Over time, increased bone thickness and strength develop in the areas of most stress to the bone. This means the type of training is very important to development of strength in the cannon bones in the appropriate areas. So, can altering conventional training methods of racing Thoroughbreds reduce or eliminate the incidence of bucked shins? It can according to research conducted by Dr. David Nunamaker and associates from New Bolton Center in Pennsylvania. He has found that young horses have higher strains on their cannon bones when running fast than do older horses. He reports that the direction of the principal strains, in Thoroughbreds, seems to change significantly with increasing speed. Training young race horses without developing bucked shins is the art of regulating the frequency and intensity of the workouts so that enough strength is built into the bones while avoiding the weakening that occurs during bone remodeling. Conventional training programs will gradually increase the exercise distance and intensity of a horse to gallops of two miles per day, with breezes at 7, 10, or 14 days, with these high speed workouts gradually increased so that the animals are breezing the distance of their race, with workouts of a half mile or more being common. Nunamaker's revised training program is aimed at decreasing the distance galloped, usually to one mile. Slow-speed jogging for conditioning is detrimental to the bone because the principal strain directions in the bone are quite different from those in the fast-working gait. Short, higher-speed workouts (breezes) are included two times a week at the end of the gallops, with the distances slowly increasing from a furlong to a half mile. A modified training program recommended by Dr. Nunamaker is provided below.

	Protocol	Intensity	Duration of STAGE:
Horse worked 6 days/week	W al ked to track Walked 1/2 mile on track Jogged 1/2 mile on track Galloped 1 mile	Daily	
STAGE I	Last 1/8 mile of gallop completed in 15 seconds	Performed 2 days a week	5 weeks
STAGE 2	Last ¼ mile of gallop completed in 30 seconds	Performed 2 days a week	5 weeks
STAGE 3	Gallop lengthened to 1 ¼ mile.	Daily	
	Breezed ¼ mile in 26 seconds.	Once a week	4 weeks
	Strong gallop added to the1/4 mile breeze for a Total time of 40 seconds.	Once a week	3 weeks

In the event that a horse has to take time off because of illness, at 10 -14 days off, a one-month backup in the training schedule is suggested, as this time off might be enough to activate bone remodeling.

The Bottom Line

High-speed exercise in small doses seems highly protective against bucked shins whereas long galloping exercise increases the risk for buck shins. So, as the old adage goes: "An ounce of prevention is worth a pound of cure."

J.D. Wheat
Veterinary Orthopedic
UCDAVIS
School of Veterinary Medicine

Department of Anatomy, Physiology and Cell Biology
School of Veterinary Medicine
University of California
One Shields Avenue
Davis, CA 95616-8732
530-752-1174; 754-0150 (FAX);

June 15, 2008

Subcommittee on Commerce, Trade, and Consumer Protection
Committee on Energy and Commerce
U.S. House of Representatives

RE: Hearing entitled, "Breeding, Drugs, and Breakdowns: The State of Thoroughbred Horseracing and the Welfare of the Thoroughbred Racehorse."

Testimony for June 19, 2008 of:

Susan M. Stover, DVM, PhD, Diplomate of the American College of Veterinary Surgeons
Professor
JD Wheat Veterinary Orthopedic Research laboratory
School of Veterinary Medicine
University of California, Davis
Davis, CA 95616

Summary

- Musculoskeletal injuries are the major cause of racehorse death and attrition.
- Racehorses are much more likely to suffer catastrophic injuries as a result of inadvertent circumstances than as a result of intentional abuse.
- Opportunities for injury prevention are great because catastrophic injuries are the acute manifestation of a more chronic process, and many risk factors are manageable.
- Racing officials have embraced scientific evidence and mandated change for the benefit of equine welfare in the face of long-standing tradition and horsemen resistance.
- There is a need for tracking the racehorse population.
- Research funds are needed to provide scientific evidence for further changes to enhance equine and industry welfare.

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Mr. Chairman and Members of the Subcommittee on Commerce, Trade, and Consumer Protection, thank-you for the opportunity to share our knowledge of racehorse musculoskeletal injuries and ongoing efforts for injury prevention.

California has monitored racehorse deaths for over 15 years. The California Horse Racing Board, a subcommittee of the California State legislature, instituted a Postmortem Program in 1990, where all horses that die at a California racetrack under the jurisdiction of the Board undergo necropsy examination by pathologists at California Animal Health and Food Safety Diagnostic Laboratories of the School of Veterinary Medicine, University of California, Davis. Racetracks transport horses to necropsy facilities in this highly collaborative program. Industry organizations (e.g., Grayson Jockey Club Research Foundation, UC Davis Center for Equine Health) fund highly competitive, in-depth research projects on racehorse injuries and illnesses, conducted by University faculty and private veterinarians. Over 4,200 racehorses have been necropsied through this program. Necropsy programs have now been established in other states, and there are efforts to standardize reporting of necropsy findings nationwide.

Musculoskeletal injuries are the greatest cause of racehorse death and attrition. In California, 79% of deaths are associated with racing and training injuries. Although most fatal injuries occur during racing, over 32% of injuries occur during training activities. From 1990 to 2006, an increasing trend was observed for injury rates. The proportion of Thoroughbred horses with a fatal musculoskeletal injury during racing and training has risen from approximately 3 horses to 5 horses per 1000 Thoroughbred race starts. The proportion of Thoroughbred racehorses with a fatal musculoskeletal injury has risen from 17 horses to 24 horses per 1000 Thoroughbred horses that started a race. Musculoskeletal injuries

resulted in 19-33% of racehorses leaving training within a 3 month or less period in the United States. An example helps us appreciate the impact of these rates of turnover on a racetrack population. For a 19% turnover in a 3 month period, approximately 2 times the daily population would be required to maintain horses at the racetrack throughout the year, assuming that horseracing occurs throughout the year and horses that leave the racetrack do not return in the same year. These trends are disturbing, especially in light of the discoveries made through the California Postmortem Program. However, there is recent evidence for a reversal in the trend for injury rates.

Pathologic evidence indicates that many catastrophic, fatal musculoskeletal injuries are the acute manifestation of pre-existing, milder injuries that develop over several weeks to months. Mild injuries are typically repetitive, overuse injuries. As with any physical activity, bone incurs microscopic damage when loaded during exercise. Normally, damaged bone tissue is continually replaced by healthy bone tissue through the repair process. Key to understanding the implications of the repair process in elite athletes is the time course of events during repair of microdamage. Much like demolition of a building, a unit of damaged bone tissue can be removed rapidly (within days to 2 weeks). However, similar to constructing a new building, the orderly replacement of a unit of bone requires months. Consequently, when the repair process occurs regionally in response to the quick accumulation of focal microdamage there is a transient period of bone weakness that occurs after damaged bone has been removed and before completion of bone replacement. The focal weakness allows initiation of a complete fracture under otherwise, physiologic training and racing conditions. Racehorses can be inadvertently susceptible to a fracture by virtue of routine racing and training conditions, that is, *without* intentional abuse.

The clinical signs preceding fracture development may be subtle and difficult to detect. Consequently, there is a need to optimize the ability to detect injuries during the early stages of development. Advanced imaging techniques and accessibility to advanced imaging equipment are

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continually improved. However, the potential for permitted medications to mask mild injury and to contribute to injury development needs to be assessed. The good news is that there is time during injury development for intervention for catastrophic injury prevention.

Injuries are multifactorial, with numerous contributing factors that create opportunities for injury prevention. Epidemiologic evidence indicates that horse characteristics (age, gender, quality), training and racing history, hoof management, horseshoe characteristics, pre-existing musculoskeletal injuries, racetrack characteristics (geometry, condition, and surface), and race features (e.g., class of race, purse) affect risk for injury. Several of these factors are likely to affect the rate of microdamage accumulation and can be managed for injury prevention. Key factors affect the magnitude and frequency of bone loading, and include exercise history, hoof conformation and shoeing, and race surface design. High exercise intensity increases risk for fatal injury and also for lay-up (inability to race). Hoof conformation and shoeing affect risk for injury because modifications can amplify loads to bones, tendons, and ligaments. Race surface characteristics affect the magnitude and nature of load transferred to the hoof.

Racing jurisdictions are actively addressing the injury problem. In fact, racehorse owners, trainers, and veterinarians; racetrack officials; and industry regulators have embraced scientific evidence and implemented changes for the benefit of equine welfare that countered long-standing traditions. Advanced imaging equipment has been installed at some major California racetracks to enhance early detection of injuries. Jurisdictions have mandated limitations on the height of a traction device, toe grabs, on horseshoes after studies demonstrated an association with increasing risk for injury with increasing height of toe grab. Recent scientific evidence demonstrated that a synthetic race surface imparts significantly lower loads and accelerations to the hoof during exercise. California mandated that all major racetracks replace traditional race surfaces with a synthetic race surface, at huge expense to racetrack management. Other racetracks have voluntarily replaced traditional race surfaces with

synthetic race surfaces. Initial, preliminary injury data support the concept that race surface design and management have large potential for injury prevention.

Racing communities are working collaboratively at a national level to address industry problems. Examples include the national summits that addressed equine welfare in 2006 and 2008 held by the Grayson-Jockey Club Research Foundation. These strategic planning sessions brought together scientists and leaders from all facets (breeding to racing, work force to management) of the racehorse industry to identify industry problems and develop recommendations for problem resolution. Summit recommendations are in various stages of implementation. Other efforts to develop and promote uniformity among rules for racing are actively underway.

However, the racing industry consists of complicated parts. I am unaware of an industry model that identifies relationships between the components of the industry. It is conceivable that management decisions inadvertently affect racehorse training and management, and thus have affects on equine health and welfare. The number of horses required to fulfill racing inventory while minimizing racehorse attrition is unknown. The underlying racehorse population is largely unknown. Medical data are difficult to retrieve.

Further scientific research is desperately needed to guide the industry. Changes/for example in racetrack surface design, are largely based on marketing factors because of sparse scientific data. Funds for research are generally limited to those generated by organizations such as the Grayson-Jockey Club Research Foundation and centers for equine health. In some states, a small portion of pari-mutuel funds is apportioned for equine research. However, research funds are sparse relative to the size of the industry. Equine research proposals are not competitive for federal funds because horses are not considered an agricultural product, nor related to human health. Dissemination of research findings should be optimized, perhaps by mandated continuing education of racetrack personnel.

Musculoskeletal injuries have a huge, adverse effect on equine welfare, and on the Thoroughbred racehorse industry. Although fatal musculoskeletal injuries have a relatively low prevalence, milder forms of these injuries have a high prevalence. There are great opportunities for intervention and injury prevention because injuries develop over weeks and months of time. Excellent candidates for injury prevention include enhancing management practices to minimize low hoof heel angle; incorporation of more frequent, shorter high speed works or races in exercise regimes; avoidance of excessive accumulation of high speed distances over short periods of time; recognition and rehabilitation of mild injuries; avoidance of use of high toe grabs; design of safer race surfaces; and

reconsideration of permitted medications. It is important to achieve uniformity of racing surface mechanical properties among racetracks and for the design of specific surface materials to meet the spectrum of environmental conditions seen by horses. Key to tracking the prevalence of injuries and the success (or lack of success) of interventions is identification of the underlying racehorse population. The industry should consider a mechanism for identification of horses that can be used for horses' medical record, location, exercise, and movement; and racetrack horse inventory. The racehorse industry and federal granting agencies need to make a substantial investment in research related to equine welfare and in mandatory continuing education of horse owners and trainers, and racetrack veterinarians.

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Recommended Penalties and Model Rule

The following are recommended penalties for violations due to the presence of a drug carrying a Category "C" penalty and overages for permitted NSAIDs and furosemide: (*All concentrations are for measurements in serum or plasma.)*

LICENSED TRAINER	Phenylbutazone (>2.0-5.0 mcg/ml)* Flunixin (>20 - 100 ng/ml) Ketoprofen (>10 - 50 ng/ml) Furosemide (>100 ng/ml) and/or no furosemide when identified as administered	Phenylbutazone (>5.0 mcg/ml) Flunxin (>100 ng/ml) Ketoprofen (>50 ng/ml) and CLASS C Violations
1st Offense (365-day period) in any jurisdiction	Minimum of a written warning to maximum fine of $500	Minimum fine of $1,000 absent mitigating circumstances
2nd Offense (365-day period) in any jurisdiction	Minimum of a written warning to maximum fine of $750	Minimum fine of $1,500 and 15-day suspension absent mitigating circumstances
3rd Offense (365-day period) in any jurisdiction	Minimum fine of $500 to a maximum fine of $1,000	Minimum fine of $2,500 and 30-day suspension absent mitigating circumstances
LICENSED OWNER	**Phenylbutazone (>2.0-5.0 mcg/ml)* Flunixin (>20 - 100 ng/ml) Ketoprofen (>10 - 50 ng/ml) Furosemide (>100 ng/ml) and/or no furosemide when identified as administered**	**Phenylbutazone (>5.0 mcg/ml) Flunxin (>100 ng/ml) Ketoprofen (>50 ng/ml) and CLASS C Violations**
1st Offense (365-day period) in any jurisdiction	Horse may be required to pass commission-approved examination before being eligible to run	Loss of purse. Horse must pass commission-approved examination before being eligible to run
2nd Offense (365-day period) in any jurisdiction	Horse may be required to pass commission-approved examination before being eligible to run	Loss of purse. If same horse, placed on veterinarian's list for 45 days, must pass commission-approved examination before being eligible to run
3rd Offense (365-day period) in any jurisdiction	Disqualification and loss of purse. Horse must pass commission-approved examination before being eligible to run	Loss of purse. Minimum $5,000 fine. If same horse, placed on veterinarian's list for 60 days, must pass commission-approved examination before being eligible to run

***If the trainer has not had more than one violation within the previous two years, the Stewards/Judges are encouraged to issue a warning in lieu of a fine provided the reported level is below 3.0 mcg/ml absent of aggravating factors.**

After a two-year period, if the licensee has had no further violations, any penalty due to an overage in the 2.0-5.0 category will be expunged from the licensee's record for penalty purposes.