Phenylbutazone in Horses: A Review

Albert A. Gabel, D.V.M., M.S.
Thomas Tobin, D.V.M., PhD.
Richard S. Ray, D.V.M., M.S., Ph.D.
George A. Maylin, D.V.M., M.S., Ph.D.

From Department of Veterinary Clinical Sciences, The Ohio State University, 1935 Coffey Road, Columbus, Ohio 43210 (Gabel, Ray); Department of Veterinary Science, University of Kentucky, Lexington, Kentucky 40508 (Tobin); and Equine Drug Testing and Research, Cornell University, Ithaca, New York 14853 (Maylin).

With additional input by: Gary P. Carlson, University of California; Jerry R. Gillespie, University of California; Jerry H. Johnson, University of Missouri; Dennis W. Milne, Ohio State University; and David Snow, University of Glasgow; and other members of the National Association of State Racing Commissioners Veterinary-Chemist Advisory Committee: Tom Finley, A.V. Villatico, Robert E. Vessey, Dr. Francis Osog, Dr. Robert Schoenfeld, Dr. Joe Solomon, Dr. Marvin Beeman, Dr. Joe O'Dea, Dr. Gene Bierhaus, and General Wayne Kester.

1. Phenylbutazone is a very effective nonsteroidal anti-inflammatory agent in horses. Through its anti-inflammatory action, it is an analgesic and an antipyretic. It is not an anesthetic.

2. Phenylbutazone does not change a horse's innate ability to race, but by relieving inflammation it may enable him to race nearer to his maximum capability.

3. Its mechanism of action is thought to be by inhibition of prostaglandins.

4. Onset of action occurs within a few hours, and optimum effect lasts for less than 48 hours after the last dose.

5. In horses phenylbutazone is safe; side effects and toxicity are rare at the usual doses.

6. In blood, phenylbutazone can be detected for 24 hours and occasionally up to 48 hours.

7. Although the quantity of phenylbutazone in the urine is not reliable for the determination of the time that the last dose of phenylbutazone was administered, reasonable estimates can be made by a comparison of the ratios of phenylbutazone to its major metabolites.

8. Trace amounts of phenylbutazone and its metabolites can be detected in urine for up to 96 hours by utilizing electron capture derivative formation and detection by gas chromatography.

9. The usual doses of phenylbutazone given on race day may interfere with the detection of other medications, depending upon analytical methods used.

Introduction

Phenylbutazone is a safe, effective nonsteroidal anti-inflammatory drug* (NSAID) with antipyretic and analgesic activity. In the recommended doses, there is no evidence that it changes a horse's innate ability to race, except to make him perform more nearly normal if he has pain due to inflammation of part of his musculoskeletal system.

Mechanism of Action

Phenylbutazone is the (NSAID) most widely used in horses. Its mechanism(s) of action is(are) not clearly understood. Studies involving the mechanism(s) of action of phenylbutazone in the horse have not been reported. Most evidence indicates that (NSAID)'s exert their action by inhibiting the biosynthesis of prostaglandins (at the last step of biosynthesis) which directly and/or indirectly mediate the inflammatory and pain response.[11,22] This inhibition probably reduces the concentration of prostaglandins in inflamed tissues.[11,22] Prostaglandins increase permeability of blood vessels and result in swelling and inflammation of tissue.[22] Prostaglandins also sensitize pain receptors in tissues to inflammatory and pain mediators: this blockade of prostaglandin formation results in reduced pain.[22] Because accumulation of phenylbutazone in the tissue is slow and the drug only prevents formation of new prostaglandins, the anti-inflammatory action of the drug develops slowly as preformed tissue prostaglandin concentrations must first decline.[4] Blockade of prostaglandin synthesis thus slowly returns the inflamed area toward normal. The analgesic action of phenylbutazone occurs directly in the inflamed tissue (not in the brain) and is directly related to its anti-inflammatory effects.

Phenylbutazone (and other NSAID) are all highly protein bound acidic drugs which accumulate in inflamed tissues (which is important for their action), but they also accumulate in the stomach, small intestine, and kidney.[4] Thus, all drugs in this group have the potential to produce lesions of the stomach, small intestine, and kidney tissue.[1] Since prostaglandins are involved in the cause of fevers, members of this group of drugs are also antipyretic. Even large doses do not reduce liver glycogen content in experimental animals, as do the salicylates.[22] Phenylbutazone interferes with several enzymes of amino acid and amino sugar metabolism.[22] It also inhibits mucopolysaccharide biosynthesis and collagen formation and uncouples oxidative phosphorylation. The other (NSAID)'s share these inhibitory properties.[22]

*Other members of the nonsteroidal anti-inflammatory group of drugs are flunixin meglumine, aspirin, ibuprofen, naproxen, flufenamic acid, fenamic acid, mefenamic acid, indomethocin, niflumic acid, and meclofenamic acid. All these drugs share the same basic mechanism of action and general pharmacology.

Clinical Efficacy

Currently, phenylbutazone is the most effective and dependable anti-inflammatory agent on the market for the equine. It is especially effective in cases of bone and joint inflammation and laminitis[6,9,13] as well as being useful in soft tissue inflammation.[13,23]

At low doses, the effect of the drug appears to be dose related.[12] In response to a single administration intravenously or orally, a dose of 4 g has an optimal effect for a 1,000-pound horse. Two grams are required daily to maintain optimal effect. First response to the drug can be seen a few hours after administration. Optimum effect is variable but occurs approximately 12 hours after administration. Intravenous injection appears to speed onset of action, on the average by about 2 to 4 hours compared to oral use.[12] Onset of action is variable after oral administration, depending on whether the horse eats before or after the drug is given.[20] Optimal clinical effect appears to continue for a variable time, usually for somewhat less than 48 hours after the last dose of the drug, depending on the dose and length of the course of treatment.[12,20] In other species, several drugs not commonly used in horses can be altered in their degradation when phenylbutazone is used with them.[22] Therefore, their duration and intensity of action change. This action has not been demonstrated in horses. Conversely, several drugs known to inhibit drug metabolism in other species have been of little or no effect on the half-life of phenylbutazone in the horse.[21]

Metabolism

Phenylbutazone is almost completely metabolized in the horse. In separate studies, only 3.7% of a 2 g/1000 lb dose was recovered in the first 24 hours,[23] and by dosing 2 g/1000 lbs at consecutive 24-hour periods, between 1 and 2% of the parent drug was recovered in the urine.[19] The principal metabolites reported in the equine are oxyphenbutazone and γ-hydroxyphenylbutazone, the "alcohol metabolite." Together, these account for about 25% of the drug administered.[19] A second minor alcoholic metabolite has been found, whose structure has tentatively been determined by nuclear magnetic resonance to be a primary alcohol.[16] Other metabolites and conjugated forms have been reported in the rat,[2] but to date 75% of the metabolites have not been accounted for in the horse.

Because the pharmacologically inactive γ-hydroxyphenylbutazone is less tightly protein bound than either phenylbutazone or oxyphenbutazone,[2] it is readily excreted in urine and is the principal metabolite found in urine (14%) after a single dose of the drug.[19] However, if dosing is continued, the proportion of the alcohol metabolite excreted drops to 6% of the dose.[19] This change in the proportion of different metabolites in the urine as dosing

proceeds is likely related to the dose-dependent kinetics of phenylbutazone due to inhibition of the drug's metabolism by one of its metabolites. Oxyphenbutazone has been shown to inhibit the metabolism of phenylbutazone in the rat and the horse.[17,21] Thus, a metabolite of phenylbutazone (probably oxyphenbutazone) becomes bound to and inhibits liver microsomal drug metabolism enzymes[2] and alters both the metabolite pattern of phenylbutazone and the plasma half-life of the drug.[20]

Blood (Plasma) Levels

Phenylbutazone is well absorbed in the horse after oral administration; a dose of 4 g/1000 lb gives peak plasma levels of about 20 μg/ml (parts per million) 5 hours after dosing. The same dose by rapid intravenous injection gives plasma levels which decline from about 30 μg/ml to 5 μg/ml at 9 hours.[20] The half-life of phenylbutazone in the horse is dose-dependent, increasing from 3.5 hours at 2 g/1000 lb to 6 hours at 8 g/1000 lb.[23] It has been reported that the plasma half-life of phenylbutazone increased after repeated doses at 2 g/1000 lb from 5.1 hours to 6.1 hours after the fourth daily dose.[19] This increasing half-life is evidence that accumulation of phenylbutazone in the body can occur the first 4 days of administration.[19] In another study, similar half-lives (5.46 hours at 3 g/1000 lb) were reported.[24] Phenylbutazone is at least 95% protein bound in plasma at therapeutic drug concentrations.[20] Thus, at plasma levels of 30 μg/ml only about 1.5 μg/ml of drug is free to interact with the drug receptors.[20] The ability of these acidic drugs to concentrate in inflamed tissues appears to be important for the mechanism of action.[4]

In the blood, phenylbutazone can easily be detected by the routine prerace blood test after more than 24 hours and can occasionally be detected up to 48 hours post-administration, especially if the horse has been medicated for several days.[25,26]

Phenylbutazone and its metabolites may interfere with analysis for unauthorized drugs in blood and urine, depending upon the concentration of phenylbutazone, the sensitivity and specificity of the analytical techniques, and the expected scope of drug coverage.[25,26,28]

Urinary Levels of Phenylbutazone and Metabolites

a. Phenylbutazone

After intravenous administration of 2 g/1000 lb of phenylbutazone, it was detected spectrophotometrically in equine urine at 31 hours but not at 48 hours.[12] In other studies, 2 g/1000 lb[19] and 3 g/1000 lb[21] of phenylbutazone resulted in detection of the drug in the urine at 24 hours by gas chromatographic methods.

b. γ-Hydroxyphenylbutazone

This metabolite appears to be excreted less rapidly than phenylbutazone but more rapidly than oxyphenbutazone.[18,20,29] After a single dose of phenylbutazone, the bulk of the material found in the urine for the first 10 hours is γ-hydroxyphenylbutazone.

c. Oxyphenbutazone

Oxyphenbutazone is the most persistent of the urinary metabolites studied to date. After 4 daily doses of 2 g/1000 lb, about 5 μg/ml of oxyphenbutazone was found 48 hours after terminating dosing.[19] In another study, oxyphenbutazone was found up to 53 hours after dosing with 2 g/1000 lb intravenously, but later urine levels were not determined.[12] Others were able to find this metabolite for at least 96 hours, using electron capture derivatives and gas chromatography following a single intravenous dose of 4 g/1000 lb.[20,28]

d. Combined Metabolite Studies

Tracer isotope ^{14}C was observed for about 65 hours in acidic equine urine and for up to 150 hours in basic urine after administration of ^{14}C phenylbutazone.[21] As no chemical identification of the ^{14}C was reported, it is difficult to relate these results to studies on specific metabolites. In horses dosed orally with increasing amounts of phenylbutazone, the drug and its metabolites were measured spectrophotometrically.[14] After 4 g orally, no traces of the drug or its metabolites were observed at 48 hours, but the drug or its metabolites were observed at 72 hours after 8 or 16 g. After 3 consecutive doses of 8 g, it took 120 hours for urine levels to fall to 0.5 μg/ml of drug or metabolites.[14] A number of studies show that the metabolite pattern in the urine is nearly constant regardless of the route or dose.[14,18,22,28,29] High levels of γ-hydroxyphenylbutazone occur between 0–15 hours postmedication. Oxyphenbutazone levels appear more slowly, exceeding the γ-hydroxyphenylbutazone levels after 12–18 hours. Following the final administration of phenylbutazone, the interrelationships of phenylbutazone and its metabolites and their decline in the urine make it possible to reasonably estimate the time of that administration up to about 48 hours.

Side Effects and Toxicity

Side effects due to phenylbutazone are unusual in horses, there being few in clinical experience or in horses in racing.

a. Local

Accidental injection of phenylbutazone into the carotid artery will cause immediate excitement, prostration, and sometimes death. Rapid intravenous injection of the undiluted solution can cause serious phlebitis since it is irritating. Extravascular injection causes severe inflammation at the site, with phlebitis, permanent occlusion of the

jugular vein in some cases, and very rarely death due to sloughing of the vein and exsanguination.

b. Behavior

Although there is no objective evidence, the observation has been made by veterinarians that a small percentage of horses, more commonly Standardbreds, will appear to be slightly sleepy or depressed by phenylbutazone, especially after recent large doses.[3,24] If this is a valid observation, it is not known whether this affects their speed in the race.

c. Systemic

Although there is often retention of water and electrolytes in man, this apparently does not occur in horses.[12] Toxicity to phenylbutazone is almost never seen in equine patients in spite of close observation and periodic blood counts done during thousands of courses of therapy.[8,13,15,24] The drug has been given at the level of 2 g orally daily for 6 months to a number of patients[13] and to others for a period of 2 to 3 years[4] with no deleterious effects clinically nor changes in the blood counts. Postmortem studies done on equine patients which have died of various diseases and injuries while receiving phenylbutazone have not revealed lesions.[13] There has been 1 undocumented report of low hematocrit and hemoglobin following "prolonged periods" of phenylbutazone administration.[27] With the usual doses of the drug in equine patients, no substantiated evidence of blood dyscrasias (untoward changes),[7] allergic skin reactions, or gastrointestinal effects[16] have been reported. Only 2 reports in the literature present evidence for toxicity. One of these is a report, with evidence of several technical inconsistencies, on a single equine patient which showed a reversible hypoplastic anemia.[7] In the other study,[14] 4 times (8 g) and 8 times (16 g) the usual daily maintenance dose was administered to 2 horses of undescribed age and health for 9 days. In these horses "some ulcers of the oral mucosa and erosions of the fundus of the stomach" were found. In 1 experimental horse after 32 days of phenylbutazone administration, the horse was euthanatized and "necrotizing phlebitis of the portal veins" was found. It is difficult to reconcile this study with the clinical experience of minimal toxicity problems with phenylbutazone in the horse. In man, these and many other toxic and side-effects are fairly commonly seen with the drug.[22] However, it continues to be widely used in man because of its efficacy.[22] It has been suggested that the apparent low toxicity of phenylbutazone in the horse is due to the short half-life when compared to that of man.[26,22]

Effect on Incidence of Horses Breaking Down

In Thoroughbred horses in California and Colorado where there is a close inspection for soundness before racing and good control of medication, the percentage of horses sustaining serious injuries requiring destruction has been the same or slightly less in horses which have been given phenylbutazone compared to those which have not been given the drug.[2,10] The incidence of serious injuries to the horses racing in these states has not increased since the controlled use of phenylbutazone has been permitted.[2,10]

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