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Pharmacology Review: The Nonsteroidal Anti-Inflammatory Drugs. I. Phenylbutazone.

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The anti-inflammatory drugs in use in equine medicine fall into two principal categories, the corticosteroids, which we have dealt with previously[11] and all the others. These other drugs are known collectively and logically as "nonsteroidal anti-inflammatory drugs" (NSAID).[5] The original member of this group is aspirin. The second oldest is phenylbutazone, which was introduced into human medicine around the time of World War II and shortly thereafter into veterinary medicine. Phenylbutazone was widely used in human medicine for a number of years,[16] but it soon became apparent that its use was associated with a small incidence of specific and serious toxicities.[6] Because phenylbutazone has caused deaths in humans from aplastic anemia and agranulocytosis, its use in human patients is now restricted. With the recognition of the therapeutic limitations of the corticosteroid derivatives and phenylbutazone, and the huge market for a good anti-inflammatory drug, drug companies have researched the nonsteroidal anti-inflammatory field thoroughly in the last 10 years. The upshot of this has been that a large number of new nonsteroidal anti-inflammatory drugs have been developed and have recently become available in both human and equine medicine.

The nonsteroidal anti-inflammatory drugs all share a number of properties which seem to be required for their anti-inflammatory action (Figure 1). All are acidic drugs, with a pKa of 4.5 or less.[2,3] The acidic nature of these drugs means that they are all between 95% and 99% bound to plasma proteins. Because of this, drugs of this group do not pass into saliva, and saliva testing is essentially useless for detection of this important group of drugs. Their acidic nature also seems to be important for their action and has led to

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ARE:

(1) HIGHLY ACIDIC DRUGS

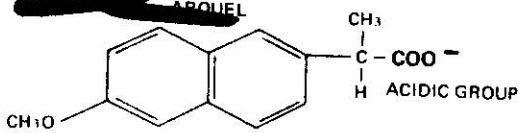
(2) HIGHLY PROTEIN BOUND IN PLASMA

(3) DIFFICULT TO DETECT IN PLASMA

(4) ACT BY INHIBITING PROSTAGLANDIN SYNTHESIS

(5) ARE LIKELY TO BE DILUTED IN URINE BY FUROSEMIDE

[illegible]UEL (SHOWN BELOW) IS A SIMPLE NONSTEROIDAL ANTI-INFLAMMATORY DRUG.



[illegible]re 1. [illegible]ti-inflammatory drugs.

suggestions that their acidity enables them to accumulate in inflamed tissues, which also tend to be acidic.[2] This accumulation would then allow them to have more effect in inflamed areas than in normal tissue. However, these agents [illegible] to accumulate in the stomach, small intestine and kidney,[1] and we will see later that the toxicities produced by these agents are usually associated with these tissues (Figure 2). Also, because prostaglandins are involved in the generation of fever, all these drugs are antifebrile or antipyretic agents (Figure 2).

Among the nonsteroidal anti-inflammatory agents, phenylbutazone remains the most popular and widely used in equine medicine. Since its introduction into equine medicine, phenylbutazone established itself as an effective anti-inflammatory agent. It soon made its appearance at the racetrack, and pressure from horsemen for permission to use it during racing

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS:

(1) INHIBIT ENZYMES WHICH FORM PROSTAGLANDINS AND THEREFORE SLOWLY REDUCE TISSUE PROSTAGLANDINS

(2) REDUCE PAIN IN INFLAMED TISSUES BY REDUCING TISSUE PROSTAGLANDIN LEVELS

(3) REDUCE FEVER (ARE ANTIPYRETIC)

(4) ACCUMULATE IN STOMACH, KIDNEY AND SMALL INTESTINES AND TEND TO PRODUCE LESIONS IN THESE TISSUES.

Figure 2. Effects of nonsteroidal anti-inflammatory drugs.

* Members of the nonsteroidal anti-inflammatory group of drugs include aspirin, ibuprofen, naproxen, flufenamic acid, meclofenamic acid, mefenamic acid, domethacin (the most potent), niflumic acid and meclofenamic acid. All the drugs share the same basic mechanism of action and the same general pharmacology. Miscellaneous nonsteroidal anti-inflammatory drugs currently used in veterinary medicine include orgotein and hyaluronic acid. Because the mechanism of action of these agents is quite distinct from the antiprostaglandin agents they are usually not thought of as typical NSAID's

increased. In 1958, Colorado approved phenylbutazone for use in racing, and the era of controlled medication was born.[b]

Phenylbutazone and the other nonsteroidal anti-inflammatory drugs produce their anti-inflammatory effects by inhibiting the production of chemicals called "prostaglandins."[14] Prostaglandins are produced in large amounts in inflamed tissues and are involved in the blood vessel changes which cause the reddening, heat, swelling, pain and loss of function that we associate with inflammation. They also have another peculiar action, in that they act to supersensitize pain receptors in the inflamed area to agents which cause pain. Anybody who has had anything as simple as a good sunburn is familiar with the great increase in sensitivity to even the lightest touch which occurs in sunburned tissue. This hypersensitivity is a typical effect of certain prostaglandins. In fact, if minute amounts of prostaglandins are injected into a normal joint, that joint soon becomes excruciatingly painful to move. This sensitizing action of the prostaglandins is represented schematically in Figure 3. It is clear from this mechanism of action that if the concentration of prostaglandins in inflamed tissues can be reduced, the signs of inflammation, swelling, and particularly the perception of pain in that area will also be reduced.

When phenylbutazone is injected intravenously it takes about 30 minutes to distribute throughout the horse and to begin blockage of formation of the prostaglandins. There are, however, unusually large amounts of prostaglandins already present in an inflamed tissue.[15] Therefore, even though the formation of new prostaglandins is blocked, phenylbutazone will not appear to take effect until these high prostaglandin levels have been reduced. This process usually takes about three to four hours, and once the excess prostaglandin has dissipated, the supersensitivity to pain reduces and the swelling and heat in the area begin to decline. Loss of these signs of inflammation will require an additional period of time, and it may take up to 12 hours or more for the full pharmacological action of phenylbutazone to become apparent.[12]

Since all the nonsteroidal anti-inflammatory agents produce their effects in more or less the same way, they all take a period of at least several hours to begin producing effects, even when they are given by intravenous (IV) injection. On the other hand, when blood levels of these drugs decline, the concentration of the prostaglandins in the inflamed tissues builds back up again, and the pain and other signs of inflam-

[b] Bierhaus, G.H.: *Personal communication*. Colorado Racing Commission Veterinarian (1979).

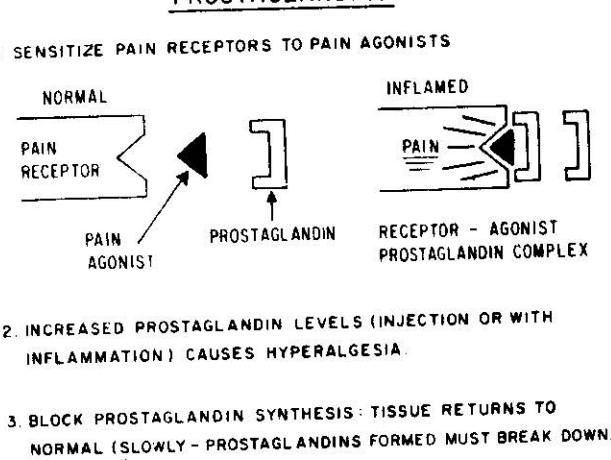


Figure 3. Sensitizing action of the prostaglandins.

mation begin to return. It is then time for another dose of phenylbutazone. It is clear from this mechanism of action that the therapeutic effects of phenylbutazone are directly related to its ability to reduce inflammation, and that any analgesic action it may have is secondary to and dependent on the anti-inflammatory effect. Phenylbutazone has no anesthetic actions and is not an anesthetic. It is simply a very effective anti-inflammatory drug, and as such, prevents the appearance of pain, which is one of the cardinal signs of inflammation.

In an average-sized horse (1000 lbs), a dose of 2 to 3 g/day of phenylbutazone IV, or about 4 g orally should produce the optimal anti-inflammatory effect. Two grams daily should then maintain the effect.[11] As the dose of the drug is increased, the blood levels increase and the plasma half-life of the drug is also increased (Figure 4).[9] If the drug is given orally instead of IV it takes about five hours for peak blood levels to be attained, and the time to attain peak pharmacological effect will be further delayed (Figure 5).[11] Urinary levels of phenylbutazone are usually higher than plasma levels of the drug, and urinary levels are detectable for at least 24 hours after a 2 g/1000 lb dose IV (Figure 6). Since the anti-inflammatory effect is not good for more than about 24 hours, daily dosing with phenylbutazone is required.[11]

For a long time the only way to assess the anti-inflammatory and lameness-alleviating efficacy of phenylbutazone was simply by "eyeballing" a treated horse. This led to some confusion about how effective the drug really was, how long it took to act, and for how long a period it was effective. Recently, however, Professor Pratt and his co-workers at the Massachusetts Institute of Technology have developed an instrument called a "force plate" which can provide an

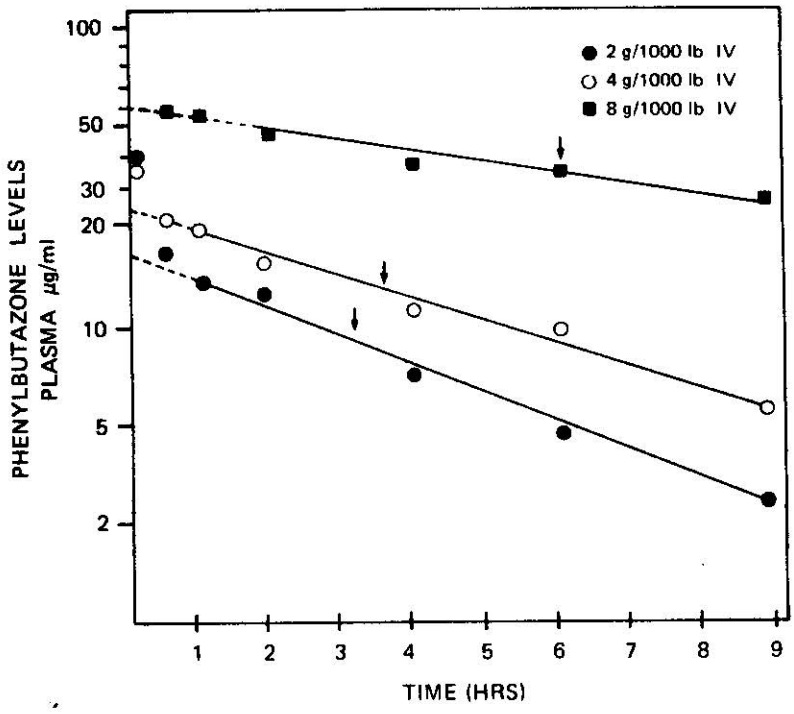


Figure 4. Plasma levels of phenylbutazone in a horse after administration of three different doses (after Piperno *et al.*).[11]

objective measurement of lameness and the effects of drugs on lameness.[12] This instrument measures small variations in the load on a horse's leg. It turns out that a horse is very unsteady on a lame leg, and that this unsteadiness, in the form of constant small readjustments of weight on this leg, can be measured by means of the "force plate." After administering phenylbutazone, the horse becomes much more comfortable and thus steadier on his sore leg, which begins to be comparable with his good leg. Using this instrument, 2 g phenylbutazone orally has been shown to take several hours to act after administration of an IV dose and to be largely over by 24 hours. If the dose is given intravenously, the onset of action is a little faster, but probably not much faster, because the reduction of tissue prostaglandins by phenylbutazone and other NSAIDs takes some time to develop.

Though the pharmacological action of phenylbutazone is over within 24 hours, the time for the animal to "eliminate" phenylbutazone is indefinite, as it is with any drug given to a horse. Since phenylbutazone is relatively easy to detect, it can be detected for a very long period indeed if the analyst so desires. Figure 7 shows some of the best data on plasma levels of phenylbutazone in the horse that has come to my attention.[10] In this experiment horses were given varying doses of phenylbutazone for up to three days, and plasma and urinary levels of the drug followed. Plasma levels started at about 20 to 30 μg/ml, declined with a half-life of about nine hours, and were still detectable in plasma eight days after dosing and, in some urine samples, on the ninth day after dosing. This experiment, when taken in conjunction with the previous data, emphasizes the point that while the pharmacological actions of phenylbutazone may be over within 24 hours, detection of phenylbutazone in plasma and urine after treatment with this drug is possible for very long periods indeed.

Although the "clearance times" for phenylbutazone in plasma and urine obviously depend on the

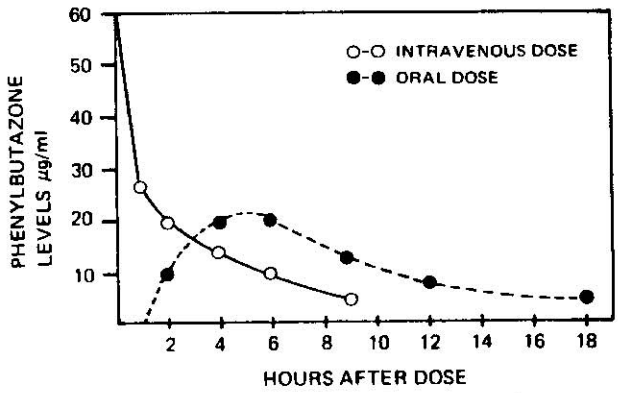


Figure 5. Plasma levels of phenylbutazone following 4 g/1000 lb (453.6 kg) administered by the oral and intravenous routes (after Piperno *et al.*).[11]

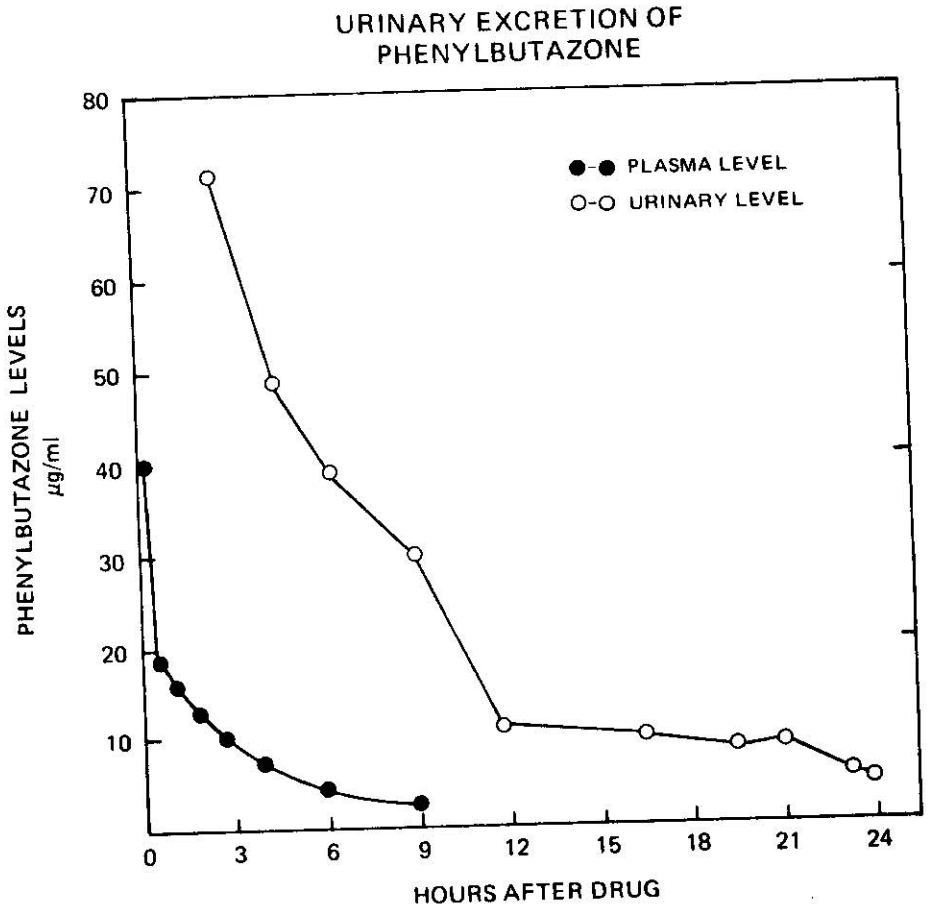


Figure 6. Plasma and urine levels of phenylbutazone in a horse following 2 g/1000 lb (453.6 kg) IV (after Piperno *et al.*).[11]

methods that the analyst elects to use, it is usually safe to assume that plasma and urine are clear by 48 to 60 hours after the last dose. Judging from the data of Figure 7 and what we know about the pharmacology of phenylbutazone, there appears to be little need for a phenylbutazone positive to be called when plasma or urinary levels of the drug are less than 1 μg/ml.

At the other end of the scale, some racing authorities have rulings designed to discourage race-day medication of horses with phenylbutazone. These rulings state that if certain levels, often 165 μg/ml, of phenylbutazone or metabolites are found in postrace urine, that this level indicates race day medication and that a "no medication on race day" rule has been infringed. In the absence of published data, the scientific status of these claims is somewhat certain, and rulings based on this information should be treated with caution.

As far as the horse is concerned, phenylbutazone is a very safe drug. The number of doses administered to horses over the years must be astronomic, while the incidence of reported side effects is small. The principal dangers with phenylbutazone are associated with its improper injection. If phenylbutazone is injected around the jugular vein by mistake, it may cause severe inflammation, abscessation, and eventual loss (sloughing) of the vein. This, however, can occur with many drugs and is a problem with the injection technique rather than with phenylbutazone. Phenylbutazone may also be injected directly into the carotid artery in the neck by accident. If this happens the horse immediately becomes excited, falls prostrate and may die. Some veterinarians and trainers report that phenylbutazone will occasionally depress a horse, especially with large doses in Standardbred horses. However, to judge from the number of horses running on phenylbutazone at some tracks, this effect must either be very rare or else horses get over it very rapidly.

There is only one single report in the literature in which horses treated with massive doses of phenylbutazone developed stomach ulcers and liver problems.[7] Thus, all in all, phenylbutazone, when administered with normal care and in reasonable doses, is a

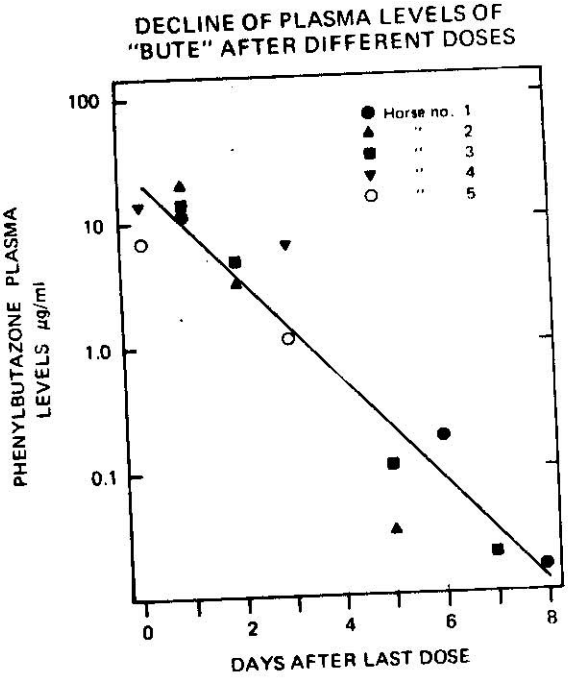


Figure 7. Symbols show plasma levels of phenylbutazone in horses which had been dosed with 2, 4, and 6 g phenylbutazone for up to three days before measurement of plasma levels. Phenylbutazone was detectable in plasma for eight days and urine for up to nine days (after Norheim *et al.*).[10]

very safe and effective drug in the horse with minimal side effects and toxicities.

This pattern of minimal toxicity due to phenylbutazone in the horse contrasts sharply with the serious toxicities seen in man. In man, some type of side effect is seen in from 10 to 40% of patients, including peptic ulcer, liver and kidney problems and, most seriously, inability to form red cells or white cells in the blood. A number of phenylbutazone-dependent deaths have been recorded, and for this reason its use is restricted in man, and it is best used only in short-term therapy.[4]

Because a dose of phenylbutazone persists a long time in the blood of man (half-life about three days) compared with its relatively short plasma half-life in the horse (six to eight hours), it has been suggested that its lack of toxicity in the horse is due to its rapid metabolism by the horse. This theory ignores observations that drug toxicities are very often due to drug metabolites rather than to the drug itself, metabolites which are of course formed at a much greater rate in the horse than in man.

The question about the effect of phenylbutazone on the performance of horses has often been raised and has not been satisfactorily answered. Reviewing the subject of phenylbutazone and furosemide[c] in racing horses, the Veterinary Chemists Advisory Committee to the National Association of State Racing Commissioners concluded that phenylbutazone does not change the innate ability of a horse to race, but by relieving inflammation may enable him to race nearer to his maximum capacity.[6] Studying the effects of phenylbutazone in time trials in horses, Sanford and his colleagues found that phenylbutazone administered intramuscularly 23 hours before "time" trials improved performance in their horses.[13] These workers were apparently rather surprised by this result and concluded that phenylbutazone had acted to relieve subclinical lameness rather than to stimulate the horses.[13] This interpretation is well supported by some experiments from our laboratory, which show no effect of phenylbutazone on fentanyl-stimulated trotting in horses, minimizing suggestions that phenylbutazone either stimulates or depresses horses at the usually used clinical doses.[1]

Another important question with phenylbutazone is whether or not it interferes with the detection of other drugs, the popularly called "masking" effect. While there is no doubt that the presence of any drug must make the detection and unequivocal identification of another drug somewhat more difficult, the consensus of the Veterinary Chemists Advisory Committee was that the usual doses of phenylbutazone given on race day may or may not interfere with the detection of other medications, depending on the analytical methods used *and, perhaps just as importantly, on what other drugs are being tested for.*[d]

[c] Lasix, National Laboratories Corporation, Somerville, NJ.
[d] Italicized portion represents this author's comments.

Part two of this review on nonsteroid anti-inflammatory drugs will appear in the July issue of The Journal.

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Viewpoints

Studies in Equine Biomechanics

James R. Rooney, D.V.M.

For those who may have missed articles recently published on *in vitro* testing of horse forelegs, I should like to summarize some of the findings.

Based on earlier *in vivo* experiments[1] it appeared that the foreleg, from just above the carpus distad, functioned largely as a passive automatic system. For the *in vitro* studies the limb was cut off above the carpus, leaving the superior check ligament-superficial flexor tendon (SF) intact, the inferior check ligament-deep flexor tendon (DF) intact, and the suspensory ligament (SL) intact. The leg was placed in a high-speed testing machine which was capable of delivering force to the leg at almost the same acceleration and in the same time as in the galloping horse. Two principal findings emerged. First, the leg *in vitro* behaved in a manner almost identical to that of the *in vivo* leg, but there was one consistent difference between the live and dead leg.

The vertical force developed by a horse galloping over a force plate buried in the racetrack is shown schematically in Figure 1. The initial bump immediately after impact is characteristic of both human and horse and is called the "heel-strike." Its exact nature is not known. Obviously, the vertical force on the foreleg rises rapidly to a maximum at midsupport and then decreases, becoming zero when the foot leaves the ground at lift-off. It may be noted that the maximum vertical force is aproximately two times the horse's body weight (i.e. for a 1000 lb horse, the dynamic load is 2000 lb).

The dead leg in the testing machine was subject to the same loading as the live leg and the curve in Figure 2 resulted. The graphic record of the vertical force is essentially identical except for the high frequency vibrations which appeared in the first moments after impact.

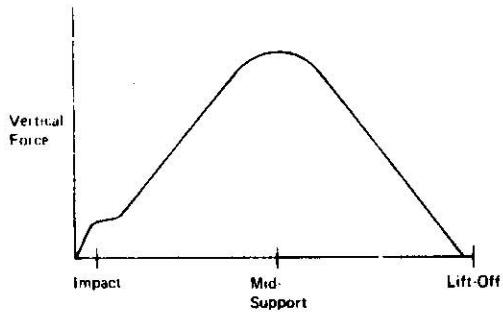

Figure 1

The conclusion is that the muscles of the foreleg serve primarily to prevent vibration of the leg immediately after impact, since vibration is not present in the live horse and is present, consistently, in the leg deprived of muscle.

The forearm muscles, then, as has been emphasized elsewhere[1,2] are not primarily concerned with movement of the leg; their primary function is to prevent movement—to prevent vibration.

(continued on page 292)