Pharmacology Review: The Nonsteroidal Anti-Inflammatory Drugs. II. Equiproxen, Meclofenamic Acid, Flunixin and Others

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In Part I of this series, we reviewed the pharmacology of phenylbutazone, the standard nonsteroidal anti-inflammatory drug used in the horse.[1] In this portion of the review we compare phenylbutazone with a number of the more recently introduced nonsteroidal anti-inflammatory drugs (NSAIDs).

Equiproxen.[a] Equiproxen is another nonsteroidal anti-inflammatory agent with analgesic and antipyretic actions. It is recommended for the relief of pain, inflammation, and lameness associated with myositis and soft tissue disease of the horse. Its therapeutic effects in the horse have been studied in some detail by E.W. Jones and co-workers.[9,10] These workers induced "tying up" in horses by injecting lactic acid into the back muscles and then studying the effects of equiproxen on length of stride, pain, lameness and tissue swelling.[9]

Length of stride in the horse is a sensitive measure of lameness, and Kilian and Jones[10] were able to show that equiproxen greatly reduced lameness caused by lactic acid injections. In the untreated horses lameness peaked at two days after injury was induced and persisted for up to 14 days, while in equiproxen-treated horses the lameness was greatly reduced and virtually eliminated within three days. Comparison of the areas under the curves for the treated and nontreated horses suggests that equiproxen treatment was at least 80% effective in reducing lameness. Similarly, equiproxen treatment had marked effects in reducing swelling, and other data showed that it also equivalently reduced pain. These data constitute the best and most clear-cut experimental work demonstrating the therapeutic effects of a nonsteroidal anti-inflammatory drug that this author is aware of, and clearly delineate the therapeutic efficacy of equiproxen.

[a] Naproxen. Diamond Laboratories, Des Moines, IA

Based on this experimental model, a study in which phenylbutazone and equiproxen were directly compared led Jones and Hamm[9] to conclude that in the equine myositis model, equiproxen was superior to phenylbutazone for more rapid relief of inflammatory swelling and associated lameness.

In other work, the response to equiproxen obtained in these studies was compared with the response in naturally occurring "tying up" disease. In the natural disease the average time for remission was found to be about five days, and a favorable response was observed in more than 90% of the animals.

Hamm[7] also evaluated the effects of continuous administrations of equiproxen during training to 50 yearling Quarter Horse colts. These colts were assigned to two equal groups at the beginning of a four-month training season, the yearlings assigned to the untreated (control) groups receiving standard medication for musculoskeletal disease as required. The test horses received about 5 g daily of equiproxen in feed during the training session. Hamm observed a marked and highly significant reduction in time lost during training and in the racing season in the horses on equiproxen, who lost only 3% of their training time compared with a 13% loss in training time in the control group. The appearance of musculoskeletal problems was delayed in the equiproxen-treated group, and when musculoskeletal problems did appear, their duration was reduced compared with the control group. The horses treated with equiproxen raced significantly more often than the control horses, and the overall frequency of musculoskeletal injuries was dramatically reduced four-fold during the training phase and 30-fold during the racing phase, for the horses on continuous equiproxen. This is very provocative data, and if independently confirmed, makes a clear case for the benefits of anti-inflammatory medication of young horses in training and in racing.

After oral administration of equiproxen the drug is about 50% absorbed. The recommended dose is 10 mg/kg or about 5 mg/lb. The plasma half-life following oral or intravenous administration has been estimated at about four hours. After oral administration, plasma levels of the drug peak at about 25 μg/ml between two and three hours after dosing and then decline to less than 1 μg/ml at 24 hours. If the drug is given twice a day, as recommended, one would then get a second peak of drug which should decline to less than 5 μg/ml by 24 hours. Equiproxen thus appears likely to have little tendency to accumulate in the horse.

Equiproxen is a very easy drug to detect in the horse because it absorbs well in the ultraviolet range, either as the parent drug or as its major metabolite, 2-(6-hydroxynapthyl) propionic acid, both of which are excreted in high concentrations in urine. The approximate half-life of these compounds in equine urine is about six hours, and it appears that at least 60 hours should be allowed for equiproxen to clear the urine of the horse.

Equiproxen appears to be a relatively safe drug in the horse, in that three times the recommended dose can be given for up to 42 days with no attributable lesions. In mares, equiproxen was administered in late pregnancy without apparent effect on the mare or the foal, and these mares were subsequently rebred and conceived normally.

Flunixin Meglumine.[b] Flunixin is another member of the NSAID family[3] which has recently been approved for use in equine practice. It appears to be more potent than other members of this group in that a dose of about 1.0 mg/kg produces good clinical effects. The pharmacology and pharmacokinetics of flunixin in the horse have been reported by Houdeshell and Hennessey.[4] These workers reported that an intravenous dose of flunixin improved lameness by 55% and swelling by 34% at 30 hours postinjection, compared with a 52% and 23% improvement due to phenylbutazone. While these results might seem to suggest that flunixin is more effective than phenylbutazone, the apparent comparison of these drugs at 30 hours postdosing may be misleading, as phenylbutazone was only effective for 24 hours in these particular studies. A more appropriate period for evaluating the relative merits of phenylbutazone and flunixin would be the times of peak drug effect, or after the horse had been on both drugs for a period. Because of the uncertainty of the times at which the actions of phenylbutazone and flunixin were compared, it is difficult to evaluate the relative effectiveness of these drugs in this study. Flunixin produced approximately the same response whether it was given orally, intravenously or intramuscularly.

Field trials with flunixin for a typical clinical spectrum of musculoskeletal disorders showed that remission of clinical signs occurred after two to three days of therapy. Overall, 40% of the horses were rated as having an excellent response, 34% as having a good response, 14% as fair, and 12% as poor. Unfortunately, no control data or positive control information with a well-characterized drug such as phenylbutazone were presented for comparative purposes.

[b] Banamine®, Schering Corporation, Kenilworth, NJ.

It is characteristic of the NSAIDs that individual members of this group are more effective in some conditions rather than other conditions. Both literature and clinical experience suggest that flunixin is particularly useful in the treatment of colic and rapidly alleviates pain and distress associated with this condition. In studies on the use of this drug in animals with predominantly spastic and flatulent colics, Vernimb and Hennessey[15] found an excellent or good response in 93% of flatulent colics, in 72% of spastic colic cases, 52% of statis colics and 60% of other types. Fifteen percent of horses showed a fair response and another 15% showed no response. The onset of the response to flunixin was also remarkably fast, about 40% of horses showing improvement in 15 minutes, and some evaluators reporting favorable changes in four to eight minutes. These are remarkably rapid changes to be induced by an antiprostaglandin agent, which, as pointed out previously, must reduce existing tissue prostaglandin levels to normal before they act. In fact, a response within four minutes, which is not more than two circulation times for the horse, must be accounted a very rapid response indeed. The duration of relief after flunixin was more in keeping with the known time course of action of this drug, and averaged six to eight hours after a single dose.

While flunixin is effective at 1.0 mg/kg, and 4.4 mg/kg of phenylbutazone is needed to produce an equivalent effect, this potency of flunixin should not in any way be taken as a particular advantage for flunixin. As far as the clinician and horsemen are concerned, potency is primarily an academic concept. What counts in the clinical setting is the quality of the clinical response and the ratio between the dose producing a good clinical response and that which produces a toxic effect. The actual number of milligrams of a drug required to produce the clinical effect is, per se, of little practical significance, as long as its use in effective doses is not associated with side effects or toxic effects.

The plasma half-life of flunixin in the horse is remarkably short, being only about 1.6 hours after its intravenoous injection. After this dose plasma levels peaked at 1.6 μg/ml, while urinary levels of the drug peaked at 60 μg/ml two hours after injection and then declined. After dosing horses with 1.1 mg/kg daily for four days, plasma levels of 2.9 μg/ml were observed, and traces of flunixin were still observed in urine 48 hours after the last dose.

Although the plasma half-life of flunixin in the horse is very short (1.6 hours), the peak pharmacological response to flunixin occurs at 12 hours after

dosing and the effect persists for 30 hours. This is an unusually long period of action for a drug with such a short plasma half-life, and may raise some questions about the mechanism of action or the active species of flunixin.

Flunixin appears to be a relatively safe drug in the horse, with doses up to five times the recommended dose for five days producing no drug related problems or toxicities.

Meclofenamic Acid.[c] Meclofenamic acid is another member of the nonsteroidal anti-inflammatory group of drugs. It is available as oral granules, reportedly quite palatable and can be mixed with the grain ration once a day. The usual dose rate is about 1.0 mg/lb of body weight for from five to seven days.[4]

Meclofenamic acid is an unusual drug among the NSAIDs in that its onset of action can be relatively slow, taking from 36 to 96 hours to develop.[4,12] After dosing with 1 g/1000 lbs in the horse, plasma levels of the drug peak within one to four hours at a little more than 1 μg/ml. They then decline with an apparent half-life of about six hours and clear the plasma by 24 hours. Because the plasma is essentially cleared after 24 hours, there is no tendency for meclofenamic acid to accumulate in plasma in the normal horse.

If meclofenamic acid is fed orally for five days, urinary concentrations of the drug run at about 25 μg/ml throughout the dosing period. After the last dose of meclofenamic acid, the drug is reportedly detectable in urine for 96 hours, although the levels are very low from 48 hours on. Again, since meclofenamic acid doses do not tend to accumulate in the body, the same rate of decline for meclofenamic acid in urine should be followed after single- or multiple-dose regimens. About 10 to 14% of the drug administered is eliminated in the urine, and it is thought that a good proportion of the drug is eliminated via the bile and feces. No data are available on the metabolism of meclofenamic acid in the horse.

In clinical trials on 304 horses suffering from osteoarthritis, navicular disease, laminitis and soft or bony tissue conditions, it was found that 78% of the cases with navicular disease improved, 76% with laminitis improved and 61% of the cases with osteoarthritis improved.[4] Since all these cases were carefully screened to exclude horses which might improve with stall rest, these improvements are difficult to compare with reported improvements on other drugs. These workers also reported that it was not possible to predict which horses would improve on meclofenamic acid and which would not.

Signs of toxicity to meclofenamic acid appear at high dose levels (6 to 8 mg/lb) and include mouth ulcers, loss of appetite, depression, edema and loss of weight. If the dosage rate is kept low (1 mg/lb), however, meclofenamic acid is a safe drug and useful in the treatment of musculoskeletal disease in the horse.

Aspirin. The oldest and best known of the nonsteroidal anti-inflammatory group of drugs is aspirin, or acetylsalicylic acid. The fact that aspirin is a household remedy and very readily available should not delude one into thinking that it is anything but a very effective drug. Aspirin has long been the drug of choice in the treatment of human arthritis, but it is unfortunately not nearly as effective a drug in the horse.

Where aspirin is concerned, nature has played a number of tricks on horsemen. The urine of horses and herbivores normally contains small quantities of salicylate. This salicylate either comes from the grass and hay that the horse ingests or is a product of the horse's metabolism.[5] Whatever its origin, the result is that it is difficult for a chemist to call a salicylate "positive," because salicylate is a natural constituent of horse urine.

While salicylate might thus seem to be an answer to the horseman's prayer, nature helped to set the record straight by making salicylate very rapidly excreted by the horse. It turns out that, as an acidic drug, salicylic acid is very rapidly eliminated in the basic urine of the horse. The half-life of salicylate in the blood of a horse with basic urine is less than one hour, so it is very difficult to maintain plasma levels of the drug.[5] Thus if you want to use salicylate effectively in the horse, you must give large doses of the drug and give them relatively close to the time at which you want the drug to take effect.

It would help considerably with the effects of salicylate if one could give aspirin intravenously or intramuscularly and in this way obtain a high blood level of the drug. However, since salicylate itself is not available as an injectable, this approach cannot be taken. On the other hand, a close relative of acetylsalicylic acid, thiosalicylate, is available and can be administered by injection.

Thiosalicylate is chemically a slightly different molecule from salicylic acid, in which an oxygen atom has been replaced with a sulfur atom. This chemical

[c] Arquel Parke-Davis and Company, Detroit, MI

change results in this particular salicylate being available in an injectable form, which means that higher blood levels and thus effective concentrations of the drug are readily attained. No information is available on the half-life of thiosalicylate in the horse, however, it is presumably much like that of salicylate itself. Thiosalicylate was once much used in some racing jurisdictions as a substitute for phenylbutazone, particularly in those states which have upper limits on postrace urinary concentrations of phenylbutazone. Unfortunately, because of the presence of the sulfur molecule, it is possible to distinguish this drug from normal salicylate, and a number of thiosalicylate "positives" have been called. Even though it makes little pharmacological sense to allow phenylbutazone and aspirin and to ban thiosalicylate, this apparently is the status of thiosalicylate in racing chemistry at the moment.

Orgotein.[4] Orgotein is the generic name adopted for drug versions of a copper- and zinc-containing metallo-protein called superoxide dismutase. In 1964 it was discovered to be a potent anti-inflammatory agent, and it was soon shown to be an enzyme, though beyond this little was understood about the mechanism of its anti-inflammatory action, other than that is was different from most of the other anti-inflammatory drugs in current use.[1]

Superoxide dismutase has recently been shown to be an intracellular enzyme which is part of the body's defense against the highly toxic $^{-}O_2$ or superoxide radical. Blood cells such as neutrophils and macrophages generate significant amounts of the superoxide radical as a killing agent in their attacks on bacteria, but these superoxides can also kill the phagocytes themselves.[13] When administered as a drug, superoxide dismutase apparently scavenges this excess superoxide radical and prolongs phagocyte life.

Clinical trials in humans have reportedly shown that orgotein is a safe, effective nonanalgesic anti-inflammatory drug. Its effects apparently take from two to six weeks to develop and persist for up to one month after termination of treatment. Orgotein may be administered systemically or, when the pathology is localized, injected into and around a site of a chronic inflammation.[11]

In Sweden, Ahlengard and co-workers[1] studied the efficacy of intra-articular orgotein in a series of cases of noninfective traumatic arthritis in horses. These workers concluded that intra-articular orgotein produced beneficial results, the effects being most marked (94% recovery) in horses which had shown lameness for less than six months, and less marked (49%) in horses which had been lame for more than two months before treatment.

Decker and co-workers[9] also reported on the treatment of 70 horses with local and/or intra-articular injection of orgotein. These workers considered the obtained response excellent, with 53 of the horses returning to racing within a few days, and some winning their races. Of 20 horses with fetlock problems, 16 responded to treatment and most of these after only a single dose of the drug.

As naturally occurring metallo-protein of high molecular weight, orgotein is not likely to enter equine urine in significant amounts. Even if it did it would be difficult to recover, detect and prove it to be of exogenous origin by currently used drug testing techniques.

Hyaluronic Acid. Hyaluronic acid is an essential component of synovial fluid and articular cartilage which has recently been introduced as an intra-articular therapy for joint problems. High molecular weight hyaluronic acid, which is the form injected into joints, inhibits lymphocyte migration and phagocytosis and also reduces the permeability of the synovial membrane. Usually between 20 and 40 mg of the sodium salt of hyaluronic acid (10 mg/ml) is injected into the joint, with an equivalent volume of synovia being removed. Reporting on a study of the effects of hyaluronic acid treatment in racing horses, Asheim and Lindblad[2] had "frequently very good effects" with hyaluronic acid. These good effects were seen in foals which had previously been point-fired, blistered and sometimes treated with intra-articular corticosteroids. These authors considered it remarkable that in most cases injection of 1 to 2 ml of hyaluronic acid was sufficient to cure the lameness. The only factors which appeared to predictably interfere with therapy were pronounced bony changes in the joint or prior treatment with costicosteroids.

The mode of action of hyaluronic acid is not clear, but it appears to persist in the joint for days after an injection. One theory is that hyaluronic acid has good surface-protecting properties. Because of its high molecular weight and the large number of electrical charges carried by hyaluronic acid, diffusion of hyaluronic acid away from an intra-articular injection site and its detection in urine by current routine screening methods is highly unlikely.[16]

In summary, reviewing the properties of the nonsteroidal anti-inflammatory drugs, it is apparent

[4] Palosein®. Diagnostic Data, Inc., CA.

that phenylbutazone is still the standard against which other drugs are compared. All these drugs share a number of broadly similar characteristics in that dosages are approximately equivalent from drug to drug, their time courses of action are broadly similar and their detection in blood or urine is not particularly difficult. There are, however, subtle differences in their clinical effectiveness against certain conditions, which makes certain agents the drugs of choice for specific conditions. In this way flunixin is apparently more effective against colic than other members of this group and is the drug of choice in this area. Similarly, equiproxen appears to be the drug of choice for muscle soreness, and is reported to be particularly effective in young horses with minor muscle problems. Meclofenamic acid has acquired a reputation for being useful in foot and hoof problems, and other specific strengths of individual members of this group will doubtlessly become apparent as clinical experience with these drugs increases. Therefore, despite the basically similar mechanism of action of the NSAIDs, they are all far from clinically equivalent, and it is a good idea to try different NSAIDs on clinical conditions which might be expected to respond to these drugs if the response to one member of this group is poor.

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