Non-steroidal Anti-inflammatory Drugs

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Basic Pharmacology and Physiologic Effects

Mechanisms of Action

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually defined as those agents that inhibit one or more reactions involved in the production of prostaglandins and thromboxanes, important mediators of the inflammatory process in many organs and tissues. They find use in horses in the supportive treatment of a variety of systemic states and painful musculoskeletal or soft tissue conditions. The principal action of most NSAIDs is the inhibition of cyclooxygenase (COX), the first in a series of enzymes responsible for the conversion of arachidonic acid to prostaglandins (Fig. 1).

Importantly, recent research has revealed that there are two forms of COX, the first which produces physiologic levels of prostaglandins in a constitutive manner (COX 1), and an inducible form of the enzyme (COX 2) which is responsible for the elevated levels of prostaglandins observed during inflammatory events in a variety of tissues. It appears that the constitutive activity of COX 1 is responsible for many of the homeostatic properties ascribed to prostaglandins and toxicity is predominately related to sustained COX 1 inhibition. Most currently available NSAIDs inhibit the activities of both COX isoforms, however the proportion of inhibition of COX 1 vs. COX 2 varies among compounds. This effect may also vary among species, and the specific anti-inflammatory profiles of most NSAIDs used in horses remain to be explored in detail. A number of selective COX 2 inhibitors are being investigated for use in treatment of a variety of diseases in humans and, in general, have shown clinical efficacy similar to that of non-specific COX inhibitors, largely unaccompanied by typical NSAID side-effects. It is likely that a similar trend will occur in equine practice, particularly when more affordable generic forms of these drugs become available.

In addition to COX inhibition, NSAIDs have other anti-inflammatory effects. For example, carprofen reduces edema and joint effusion in experimental joint disease models in horses by a non-COX mediated pathway and it has been reported that ketoprofen inhibits both lipoxygenase and COX (Fig. 1). Moreover, at least some NSAIDs are capable of inhibiting elements of cellular inflammation. Thus, it is clear that a number of NSAIDs possess anti-inflammatory actions other than COX inhibition, however the biologic significance of these effects are not clearly defined and may occur only at tissue concentrations achieved by exceeding regularly used dose rates. These side actions may also prove to complicate the premise that selective COX 2 inhibitors are devoid of side effects, particularly when used

NOTES
at higher dose rates where effects unrelated to COX inhibition are evident.

Pharmacokinetics and Detection Limits

At present, phenylbutazone is the most popular and economical agent used in horses, and its clinical efficacy appears to compare favorably with other NSAIDs.13 Popular alternatives include flunixin meglumine, meclofenamic acid, naproxen, ketoprofen, and carprofen. Much of the data that exists regarding the pharmacology of these and other NSAIDs in horses is the result of work conducted at the Royal Veterinary College and a thorough review has been recently published.14 Among the numerous contributions of this group is the distinction between tissue and plasma levels of phenylbutazone. Specifically, the clearance of phenylbutazone from acidic (inflamed) tissues is slower than plasma elimination, indicating that therapeutic effects of phenylbutazone may persist in tissues after plasma levels have decreased to negligible levels.15 This finding has prompted re-examination of the previously held concept of therapeutic plasma concentrations of phenylbutazone of 5–15 \( \mu g/ml \),16 and has biologic consequences with respect to the performance in some treated horses.

Pharmacokinetic data is available for many of the common NSAIDs used in horses and approximate detection limits have been determined and published by Agriculture Canada (Table 1).17 It should be noted, however, that there is considerable variation in the pharmacokinetic profiles of NSAIDs between horses and clearance influenced by a variety of factors such as dose, the presence or absence of local inflammatory conditions, and feeding schedule (for orally administered drugs).18–21 The latter effect can be of particular importance in estimating withdrawal times, given that the peak plasma concentration and apparent half-life can be substantially delayed when NSAIDs are given to horses having access to hay. Collectively, these biologic factors, combined with evolving methods of drug detection, will continue to hamper the determination of precise withdrawal times.

Presently, there is not an abundance of information on comparative aspects of the potency, efficacy, and tolerability of NSAIDs, and the biologic reasons for clinical impressions of relative efficacy are yet to be defined. Clinical selection of a particular NSAID is governed by considerations of the desired therapeutic effect (combating endotoxemia, ameliorating pyrexia, antithrombotic effects, analgesia) and the organ system affected. The dose rates, formulations, and relative cost of several commonly used NSAIDs are pro-

![Figure 1. The arachidonic acid cascade. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the generation of prostaglandins largely by inhibition of one or both forms of cyclooxygenase (COX 1 and COX 2). Toxicity of NSAIDs is predominately due to inhibition of the constitutive or “housekeeping” form of the enzyme COX 1. Certain NSAIDs may also inhibit the generation of leukotrienes by inhibiting the lipoxygenase portion of the cascade.](image-url)
provided in Table 2. Regardless of the specific choice, it is important to note that the concentration of many NSAIDs required to produce analgesia is often lower than that producing anti-inflammatory effects, so that NSAIDs can often be titrated to a minimal effective dose, thus reducing the occurrence of problems related to NSAID toxicity.

NSAID Toxicity

Toxic effects of NSAIDs are well-known and have been thoroughly characterized for a number of available compounds. Toxicity is correlated to plasma concentration of drug and is largely a result of COX 1 suppression and the consequent dearth of the "physiologic" levels of prostaglandins. For example, prostaglandin E2 (PGE2) plays an important role in protecting the gastrointestinal tract from ulcers by a number of mechanisms and co-administration of synthetic PGE2 is protective for phenylbutazone-induced ulcers. The common manifestations of NSAID toxicosis are outlined in Table 3.

Osteoarthritis—Model of NSAIDs’ Beneficial and Deleterious Effects

NSAIDs are used for a myriad of traumatic, inflammatory, and septic conditions, and the general beneficial and deleterious effects are similar. Traumatic and degenerative joint disease are common problems for all types of equine athletes and global considerations of the biology of these drugs at a tissue, cellular, and systemic level can be exemplified using osteoarthritis as a model. Recent findings also serve to illustrate that the biologic role of

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name(s) (USA)</th>
<th>Formulation(s)</th>
<th>Recommended Dose (mg/kg)</th>
<th>Relative Price/Day (May 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenybutazone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Phenylbutazone injection, Bizolin 200, Equipalazone Equi phen paste etc.</td>
<td>Tablets, Paste, Granules/powder, Injectable (IV only)</td>
<td>4.4 twice on day 1, 2.2 BID (4 days), then 2.2 SID (IV, PO)</td>
<td>Tablets (1 gm), Paste (12 gm), Injectable</td>
</tr>
<tr>
<td>Flunixin meglumine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Banamine, Citation, Equinone, Meflosyl etc.</td>
<td>Granules, Paste, Injectable</td>
<td>1.1 daily for 5 days (IV, IM, PO), then 2.2 SID or less (PO)</td>
<td>Granules (500 mg envelope), Paste (1500 mg tube), Injectable (50 mg/ml)</td>
</tr>
<tr>
<td>Meclofenamic acid&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Arquel</td>
<td>Granules</td>
<td>2.2 SID (5–7 days), then 2.2 SID or less (PO)</td>
<td>Dose = (2.2 mg/kg SID)</td>
</tr>
<tr>
<td>Naproxen&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NM</td>
<td>Tablets</td>
<td>10 SID for up to 14 days (PO)</td>
<td>Tablets (500 mg)</td>
</tr>
<tr>
<td>Ketoprofen&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ketofen</td>
<td>Injectable</td>
<td>2.2 SID (IV)</td>
<td>Dose = (2.2 mg/kg SID)</td>
</tr>
<tr>
<td>Carprofen&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rimadyl&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Injectable</td>
<td>0.7 SID (IV)</td>
<td>Tablets (100 mg)</td>
</tr>
</tbody>
</table>

NM = Not currently marketed by veterinary distributors in USA.
<sup>a</sup>Enolic acid.
<sup>b</sup>Carboxylic acid.
<sup>c</sup>Only available in tablet form in USA.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Side Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Ulceration of gastric glandular and large colon mucosa</td>
<td>Toxicity may be due to direct effects of drug in addition to COX 1 inhibition.</td>
</tr>
<tr>
<td>Renal</td>
<td>Necrosis of renal papillae</td>
<td>Considered due to renal medullary ischemia related to conditions in which prostaglandins regulate renal blood flow.</td>
</tr>
<tr>
<td>Vascular</td>
<td>Thrombophlebitis; Perivascular injections of phenylbutazone</td>
<td>Phlebitis at sites other than the injection site may contribute to renal and pulmonary vasculitides.</td>
</tr>
<tr>
<td>Bone and Cartilage</td>
<td>Inhibition of cartilage matrix synthesis and accelerated joint destruction in osteoarthritis</td>
<td>A variable effect. Some NSAIDs have been shown to have chondroprotective effects in some studies.</td>
</tr>
</tbody>
</table>

*Early signs of toxicity include depression, anorexia, and decline in plasma protein concentration.
prostaglandins and the effects of NSAIDs are considerably more complex than previously thought.

Prostaglandins and Joint Metabolism
In addition to a plethora of other inflammatory mediators, prostaglandins are found in elevated concentrations in diseased joints and have been linked to synovial inflammation and cartilage matrix depletion.33,34 While the specific effects of prostaglandins on joint metabolism are unclear, it is widely held that PGE2 contributes to the lesions of osteoarthritis. The synovial membrane and articular cartilage are both capable of synthesizing PGE2, and elevated levels of PGE2 have been demonstrated in the synovial fluid of affected horses.25,26 PGE2 has been implicated in the erosion of cartilage and bone27 and it has been suggested that prostaglandins may actually modulate the release of metalloproteases such as collagenases and stromelysins; enzymes considered pivotal in the degeneration of cartilage matrix in osteoarthritis.28,29 Conversely, there is increasing evidence suggesting that matrix metalloprotease expression in articular cells is inhibited by E-series prostaglandins,30 data that are supported by recent studies using equine tissues.31 Thus, establishing the true role of prostaglandins in osteoarthritis is critical because NSAIDs receive such widespread use in the disease and their indiscriminate use can have profound systemic side effects. Once the precise role of prostaglandins in joint disease is known, it may be possible to more accurately characterize the influence of NSAIDs on joint health.

NSAIDs and Joint Metabolism
The protective and potentially deleterious effects of NSAIDs on articular cartilage have been investigated in vitro, however the clinical relevance of the results are not clear. Concern over the potential unfavorable side effects of these agents was prompted by the observation that aspirin inhibited proteoglycan synthesis and could encourage cartilage destruction32,33 and that ibuprofen was implicated in accelerated joint destruction in human osteoarthritis patients.34,35 Fears of enhanced rates of cartilage degradation with their use have not been borne out in a number of clinical and experimental studies.36,37 Recently reported protective effects of E-series prostaglandins on matrix metalloproteinase expression suggest that it is possible that the deleterious effects on joint metabolism conventionally attributed to NSAIDs may be from suppression of protective effects of prostaglandins rather than a direct toxic effect on cartilage metabolism. Indeed, NSAIDs have shown to be chondroprotective in some osteoarthritis models,38,39 however there is considerable variability in this effect. While many studies have focused on direct inhibition of degradative enzymes, potential benefits of NSAIDs may result by the suppression of other mediators of the process.40,41 In one of the few studies using equine tissues, phenylbutazone appeared to be capable of limiting the proteoglycan depletion that accompanies in vitro cartilage culture,42 but appears not to be an effect mediated by stromelysin inhibition.43

Symptomatic Effects of NSAIDs
NSAIDs are the most commonly prescribed drugs for the treatment of pain and inflammation in humans and the same is probably true in the horse. As prostaglandins are not the sole mediators of the pathophysiologic events and attendant pain in inflammatory processes, it is understandable that NSAIDs have certain limitations with respect to their analgesic and anti-inflammatory potency. In the context of the working performance horse, the principal consideration is symptomatic relief of mildly inflamed or injured tissues.

Pain relief from NSAIDs is mainly, but not exclusively, related to COX inhibition. It should be noted that prostaglandins themselves do not produce pain, except when present in large quantities.44 Thus, NSAIDs' main actions occur at sites of inflammation, where they reduce the concentrations of PGE2. Prostaglandin E2 is known to sensitize nerve endings to mechanical stimuli and amplify the chemical activation of pain receptors by other inflammatory mediators such as bradykinin and histamine, both of which act to lower the pain threshold.45,46 Because NSAIDs' principal action is to reduce the “hypersensitizing” effects of prostaglandins in inflamed tissues, they are poor analgesics for noxious stimuli applied to normal tissues compared to narcotics and local anesthetics. While most of their analgesic effects are related to COX inhibition, other mechanisms exist for some NSAIDs as exemplified by the fact that the R-enantiomer of flurbiprofen is a weak COX inhibitor compared to its D-enantiomer but has comparable analgesic potency.47 Additionally, the COX inhibitory activity of NSAIDs is not always closely correlated with analgesic potency.48 Reducing prostaglandin levels also appears to modulate pain perception centrally, an effect on spinal receptors distant from sites of inflammation49 and NSAIDs may contribute to analgesia by inhibiting sensory neurotransmitter synthesis at a spinal level.50

NSAIDs as Performance-Enhancing Drugs
Because NSAID use is ubiquitous and permitted in many racing jurisdictions and other national governing bodies (e.g., American Horse Show Association), the potential for NSAIDs to be used in a manner which could either unfairly enhance performance or contribute to injury is a logical concern. Whether or not NSAIDs are “performance-enhancing” agents remains a controversial issue depending in no small part on the definition of enhanced performance. Proponents of the use of NSAIDs in competition consider their use a means by which the horse may realize its innate
potential, as opposed to a means of surpassing its natural ability. Critics maintain that the potential of masking the pain of previous trauma significantly augments the risks of breakdown or other severe injury to the horse which could also involve riders or drivers. Philosophical considerations aside, there has not been an abundance of objective research conducted on the influence of NSAIDs on performance in normal horses. Attempts to correlate exercise-tolerance related indices (e.g., heart rate and lactate) using therapeutic doses of phenylbutazone and flunixin have yielded no compelling evidence of improved performance in normal horses.51

Perhaps the controversial issue of performance enhancement is best addressed by examining available pharmacokinetic and pharmacodynamic data in light of current regulations concerning NSAID use in racing and sport horses (Tables 4, 5). Unfortunately, this is not easily accomplished because of the poor correlation of plasma and tissue levels of NSAIDs, given the aforementioned property of accumulation in inflamed tissues. Nonetheless, attempts to correlate clinical effects with plasma concentrations of NSAID have been conducted using an experimental synovitis model.52 Using this model, a plasma EC50 (dose corresponding to 50% maximal improvement in selected clinical indices of inflammation) of 3.6 μg/ml was observed for phenylbutazone and 0.93 μg/ml for flunixin.52 It has been shown that substantial COX inhibition at inflammatory foci may occur with serum phenylbutazone concentrations of less than 1.0 μg/ml.53,54 In conclusion, a clinically relevant, therapeutic effect is quite possible in “sore” horses treated with phenylbutazone and flunixin at dose rates resulting in

### Table 4. North American Regulations Concerning Use of NSAIDs in Racehorses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Permitted Level (plasma/serum)</th>
<th>Jurisdiction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NSAIDs</td>
<td>None</td>
<td>Canada</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Not specified</td>
<td>New York, Kentucky, Ohio</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>&lt;2 μg/ml</td>
<td>Maryland</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>≥2.2 μg/ml</td>
<td>Illinois, Iowa</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>≥2.5 μg/ml</td>
<td>New Jersey</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>≥3 μg/ml</td>
<td>Arkansas, Minnesota, Indiana, Michigan, Nebraksa, Nevada, Pennsylvania, Texas, Washington, West Virginia</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>&lt;5 μg/ml</td>
<td>Florida, New Mexico</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>≥5 μg/ml</td>
<td>California, Colorado, Indiana, Michigan, Nebraksa, Nevada, Pennsylvania, Texas, Washington, West Virginia</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>≥165 μg/ml (urine)</td>
<td>Massachusetts</td>
</tr>
<tr>
<td>Flunixin meglumine</td>
<td>≤10 ng/ml</td>
<td>Pennsylvania</td>
</tr>
<tr>
<td>Flunixin meglumine</td>
<td>≤0.5 μg/ml</td>
<td>California</td>
</tr>
<tr>
<td>Flunixin meglumine</td>
<td>&lt;1 μg/ml</td>
<td>New Mexico</td>
</tr>
<tr>
<td>Flunixin meglumine</td>
<td>≥1 μg/ml</td>
<td>Nevada</td>
</tr>
<tr>
<td>Melclofenamic acid</td>
<td>≤1 μg/ml</td>
<td>Washington</td>
</tr>
<tr>
<td>Naproxen</td>
<td>≤5 μg/ml</td>
<td>Washington</td>
</tr>
<tr>
<td>Salicylates</td>
<td>750 μg/ml (urine)</td>
<td>California, Texas</td>
</tr>
</tbody>
</table>

NSAID = Nonsteroidal anti-inflammatory drug.

*Most jurisdictions do not publish regulations concerning the use of NSAIDs other than those listed.

**From available federal and state sources May, 2000.

*Cannot be administered less than 48 hr before racing.

**Or the metabolite oxyphenbutazone.

**Prohibited in 2-year-olds.
blood levels at or below those adopted by a number of racing jurisdictions and show horse regulatory bodies, however it seems unlikely that the benefits for horses free from inflammatory musculoskeletal conditions are great.

References

42. Jolly WT, Whittem T, Jolly AC, et al. The dose-related effects of phenylbutazone and a methylprednisolone acetate formulation (Depo-Medrol) on cultured explants of equine...


