Joint Therapy: Non-Steroidal Anti-Inflammatory Drugs

Michael W. Ross, DVM, Diplomate ACVS

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the medical management of horses with osteoarthritis (OA) and many other degenerative conditions as well as horses undergoing surgery. NSAIDs are given orally, parenterally, or topically; most have clinical sign-modifying effects, but some have disease-modifying effects. NSAIDs inhibit one or more of the enzymes involved in the production of prostaglandins (PGs) and thromboxanes, the so-called arachidonic acid cascade (AAC). PGs are associated with synovitis and cartilage matrix depletion, particularly those of the E series, and PGE₂ was identified in the synovial fluid of horses with OA.¹⁻⁵ PGE₂ is synthesized in synoviocytes and chondrocytes after exposure to inflammatory mediators, was implicated in the erosion of cartilage and adjacent bone, and may modulate metalloproteinase release.¹ Interestingly, PGE₂ may be involved in regulatory functions within an inflamed joint, and inhibition may produce a paradoxical response.¹ Although inhibiting PGE₂ may be advantageous in horses with OA as a clinical sign-modifying outcome, there may be long-term detrimental sequelae.¹,³,⁶ In horses, initial studies revealed no deleterious effects of NSAIDs on articular cartilage metabolism,⁷ but when phenylbutazone (PBZ) was given to horses for 14 days and serum was tested in a cartilage explant model, there was decreased proteoglycan synthesis similar in degree to that seen when interleukin-1β was given.⁵,⁸ In addition, systemic side effects of some NSAIDs have become well-recognized, and the therapeutic range may be considerably more narrow than was once thought (see below).

All NSAIDs work by inhibiting cyclooxygenase (COX), an enzyme found in the AAC that converts arachidonic acid to PG or thromboxane. Some have non-COX effects. Carprofen reduces edema and effusion in horses with experimental OA, and ketoprofen inhibits lipoxygenase in addition to COX.¹,⁹,¹⁰ However, the predominant effect is COX inhibition. There are two isoenzymes of COX, COX-1 and COX-2, that have important differences. Differential inhibition of these isoforms may well explain not only clinical efficacy of NSAIDs but also the toxic side effects leading to narrow therapeutic indices. COX-1 is known as the housekeeping form of the enzyme, because it is responsible for the production of PGs in a constitutive manner. Constitutive activity of COX-1 helps maintain homeostasis in the gastrointestinal tract (gastric mucosa and various portions of the colon) and kidney. Therefore, inhibition of COX-1 explains many of the potential
toxic side effects associated with NSAID administration. COX-2 is the inducible form of COX and is principally involved in the inflammatory events leading to elevated levels of PGs found in OA and other inflammatory processes. Thus, COX-1 could be considered the good isoform, and COX-2 could be considered the bad isoform.5 Non-selective inhibition of both COX-1 and COX-2 may indeed reduce clinical signs associated with OA but at the risk of potentiating toxic side effects. The ubiquitous drug PBZ is the best-known non-selective COX inhibitor, and although it is effective, it has potential for toxic side effects as a result of COX-1 inhibition. Selective inhibition of COX-2 while sparing COX-1 would seem ideal, and recently, the COX-2 inhibitor firocoxib was approved for equine use and was shown to highly favor COX-2 inhibition. Concentrations of firocoxib required to inhibit 50% of COX-1 activity were 384, 58, and 643 times, respectively, the concentrations required to inhibit 50% of COX-2 activity in the dog,11 cat,12 and horse,13 and when firocoxib was given to horses with naturally occurring OA, results compared favorably with PBZ.14 Compared with horses given firocoxib, horses given flunixin meglumine (FM; a non-selective COX inhibitor) had significantly lower transepithelial resistance and higher lipopolysaccharide permeability in ischemic-injured jejunum, indicating that a specific COX-2 inhibitor may be advantageous.15 The use of a combination of PBZ and FM was more effective at alleviating lameness than was PBZ alone, indicating that combining non-selective COX inhibitors had superior clinical sign-modifying effects.16 However, in an earlier study, Reed et al.17 showed the need for substantial caution in horses being administered this combination therapy, because one horse was euthanized likely as a result of toxic side effects and other experimental horses developed gastric ulcers.17 Beneficial effects of a combination of NSAIDs may be outweighed by deleterious systemic side effects.

2. Drugs and Clinical Use

The most common NSAIDs used are those given parenterally or orally (PBZ, FM, ketoprofen, naproxen, carprofen, and firocoxib) and a topically applied medication, diclofenac sodium. A review of NSAIDs and additional information can be found elsewhere.1,5,18

PBZ

In my opinion, horses are PBZ-deficient. This statement reflects my attitude to the administration and usefulness of this ubiquitous NSAID. In my opinion, PBZ is the best and most cost-effective NSAID available and has been used for nearly 30 yr safely and effectively. The toxic side effects are well-recognized in ponies,19 which seem to be particularly sensitive to the effects of non-selective COX inhibitors and caution should always be used. Certain draft breeds, such as the Clydesdale, may be particularly susceptible to the effects of NSAIDs, particularly if the horse has other systemic diseases; although on a milligram per kilogram basis, a total dose of 4 g may seem low, it was recommended that this total dose not be exceeded and the drug be given a maximum of 5–7 days.19 Horses, like ponies, are at risk to develop toxic side effects as well, including hypoproteinemia, anorexia, neutropenia, renal papillary necrosis, gastric ulceration, and right dorsal colitis.18,20,21 Recently, horses given PBZ at a relatively high dose of 8.8 mg/kg, q 24 h, PO, for 21 days developed hypoproteinemia, neutropenia, changes in right dorsal colon arterial blood flow, and changes in volatile fatty acid production.22 Although I have been cavalier in the past regarding use of PBZ, I have adjusted my recommendations based on my own experience and that of others. I believe horses at risk include hospitalized horses being managed for other serious problems such as enteritis, metritis, laminitis, and infectious arthritis; also, dehydrated horses are at substantial risk to develop renal or gastrointestinal complications and should be rehydrated before administering NSAIDs such as PBZ. Endurance horses developing exhausted horse syndrome or severe rhabdomyolysis are at profound risk of developing renal damage if NSAIDs are administered before they are given IV fluid therapy.23 Horses with OA or degenerative conditions such as navicular syndrome or horses undergoing surgery can safely receive 4.4 mg/kg, q 12 h, IV or PO for 2–3 days and then receive a tapering dose, leveling out to 2.2–3.3 mg/kg, q 12 h, IV or PO. PBZ is quite effective at managing pain associated with chronic OA, and it is my opinion that the potential deleterious side effects on cartilage metabolism are overrated; it is the continued use of the horse that poses the biggest risk to additional deterioration of the original condition. Interestingly, in a recent study, PBZ administration to horses caused a significant increase in the biomarker osteocalcin, a finding suggesting that PBZ exerted an undetermined anabolic effect on periartricular bone or a transient induction of osteogenesis in articular chondrocytes or mesenchymal subpopulation of synoviocytes.24 In hospitalized horses undergoing major orthopedic procedures, PBZ can be given chronically and safely at a dose of 3.3 mg/kg, q 12 h. Clinicians often try to wean the horse off the medication or taper the dose, leading to a notable deterioration in the horse’s clinical signs. After lameness increases, the knee-jerk reaction is to re-establish the original higher dose of PBZ; however, many horses remain lame, despite receiving a level of medication on which they had previously been comfortable. I have no explanation for this paradoxical response. To combat the potential serious or fatal sequelae of contralateral laminitis, I prefer to risk the potential side effects of PBZ therapy and often maintain horses on relatively high doses. Others disagree and recommend no more than 2.2 mg/kg, q 12 h be administered after an initial load-
ing dose of 4.4 mg/kg, q 12 h for no more than 2 days.18 In combination with intra-articular medications and topical application of NSAIDs, parenteral or oral PBZ therapy is quite effective in the medical management of OA. Corrective shoeing significantly increased the peak vertical ground reaction force (a measure of increased weight bearing expressed as the percent of the body weight force) in horses with navicular syndrome; the addition of PBZ therapy but not intra-articularly administered triamcinolone acetonide produced a significant additional increase in weight bearing.25 Drug testing rules often preclude use of the medication at a dose sufficient to alleviate clinical signs in upper-level sports horses and racehorses. However, PBZ therapy is often quite useful in racehorses in which low-grade exercise is given in an attempt to work through mild pain, gait deficits, and poor performance associated with mild OA or subchondral bone pain. PBZ therapy may help prevent the development of compensatory lameness. There has long been an attempt to link the chronic low-grade administration of NSAIDs, such as PBZ, FM, and naproxen, to fatal or non-fatal musculoskeletal injuries. In a recent study, the possible relationship of NSAID administration and injuries in Thoroughbred racehorses was investigated; plasma concentrations of PBZ and FM but not naproxen were higher in injured horses, but Dirikolu et al.26 concluded that additional study was needed. A combination of PBZ and other NSAIDs such as FM could be used to manage substantial musculoskeletal pain in horses, but potential toxic side effects must be strongly considered.16,17

Route of administration seems to be important. The response of horses given PBZ IV seems superior compared with the response of horses given the drug orally. Lameness is often worse in horses with substantial pain switched from IV to oral administration (usually hospitalized horses with severe OA, laminitis, or other substantial injuries). The same dose given orally does not produce the same clinical results, and it seems that bioavailability is considerably less when PBZ is given by the oral route.

FM Half-life of FM is reported to be much less than PBZ (PBZ = 5.5 h18 and FM = 1.6–2.5 h18), and inexplicably, it is most often only given one time daily.18 The medication is given orally (chronically), much like PBZ. There has been concern about possible myonecrosis associated with IM use.18 I have occasionally seen horses develop clostridial myositis after IM injection, and one of these cases was early in my career; therefore, I have avoided this route of administration. The drug is thought to be safer than PBZ and similar in effect. My experience is different, and FM does not seem to work as well as PBZ, particularly when given one time daily. I have used the drug in combination with PBZ in horses with severe lameness for 2 or 3 days, but there is risk to the development of toxic side effects (see above).17 Because the drug is more expensive and less efficacious, I seldom recommend it in horses with OA.

Ketoprofen Ketoprofen inhibits both the COX and lipooxygenase pathways in the AAC and thus, should be more effective than COX inhibitors, because the drug should reduce leukotriene in addition to PG accumulation. However, numerous studies have refuted this claim.18 Given that ketoprofen is poorly absorbed when given orally, is more expensive than PBZ, and anecdotally, does not alleviate clinical signs as well as PBZ, I do not recommend it. In a study comparing PBZ with ketoprofen, PBZ was superior to ketoprofen in managing acute synovitis.18,29

Naproxen Naproxen would seem to be an ideal substitute to PBZ for horses being managed chronically for OA or other degenerative conditions, but I have little experience with the drug. A review can be found elsewhere.18 Given the half-life of 4–5 h (similar to PBZ), wide safety margin, and favorable results compared with PBZ in an induced model of myositis, it seems to be a useful alternative NSAID to use.18 The dose is 10 mg/kg, q 12 or 24 h, PO.18 Naproxen may be indicated in horses that cannot tolerate PBZ because of hypoproteinemia and oral or gastric ulceration.

Carprofen Carprofen is another NSAID that inhibits both COX-1 and COX-2, although the specific mode of action has not been clearly defined.18 Anecdotal information suggests that the drug may preferentially inhibit COX-2 more than COX-1, because clinical signs of PBZ toxicity (elevated creatinine levels and diarrhea) subsided when horses were subsequently given carprofen.5 The drug is quite effective in dogs being managed for chronic OA and may have a role in the management of horses with chronic OA, although expense may be a limiting factor. Compared with etodolac, meloxicam, and butorphanol, dogs treated with carprofen showed the greatest improvement in vertical ground reaction forces and weight-bearing scores in an induced synovitis model.30 Carprofen exists as two enantiomers (R and S), and although its mechanism of action may not be completely understood, in one study, the S-enantiomer had a greater effect than the R-enantiomer or hyaluronan in stimulating proteoglycan synthesis.31 Furthermore, carprofen had an antiarthritic effect in yet another study; the drug significantly decreased PG_E2 production, antagonized an interleukin-1–induced increase in PG_E2 production, and increased proteoglycan synthesis.32 In a study evaluating postoperative analgesia in horses, there was no difference in pain score be-
between horses given carprofen, PBZ, and FM. In that study, duration of analgesia for carprofen (11.7 h before redosing) was between FM (12.8 h before redosing) and PBZ (8.4 h before redosing). Carprofen seems well-tolerated at the recommended IV or oral dose of 0.7 mg/kg, but it should not be given IM because of a risk for myonecrosis. I have no experience with the drug in horses, but given what appears to be not only clinical sign-modifying but also disease-modifying effects, consideration for its use should be given.

Firocoxib

Firocoxib is a member of a new class of NSAIDs known as coxibs that are essentially selective COX-2 inhibitors, because COX-2 inhibition is basically 643 times that of COX-1 inhibition. Pharmacokinetics and dosing recommendations for firocoxib were determined. In a recent study, firocoxib was effective compared with the vehicle control in horses with naturally occurring OA. Interestingly, in that study, no treatment-related adverse effects of either drug were found, although the dose of PBZ was modest (2.2 mg/kg, q 24 h, PO). Furthermore, the time interval between drug administration and examination was not controlled. Given the short half-life of PBZ (5.5 h) and prolonged half-life of firocoxib (>36 h), some suggest that the inconsistency in time interval between PBZ administration and clinical examination may have falsely lowered the drug's efficacy, because PBZ is more commonly administered q 12 h than q 24 h. Although evidence-based information suggests that firocoxib is similar to PBZ in clinical sign-modifying effects in horses with OA, anecdotally, the drug seems inferior in efficacy and is much more expensive.

Diclofenac Sodium

A topically applied liposomal suspension containing 1% diclofenac sodium is now approved for use in horses. Topical application was reasoned to reduce the chances of systemic side effects of the drug, although the drug is used widely in people and relatively well-tolerated. To my knowledge, diclofenac sodium has not been given to horses by other routes. Topically applied diclofenac sodium is slowly absorbed into SC tissues when enclosed in liposomes, where there is local anti-inflammatory action as a result of COX inhibition. Although the drug is slowly absorbed and clinically relevant blood and distant tissue concentrations are low, they can still be detected in both serum and urine, and these residues must be taken into account in horses undergoing drug testing. In a double-blinded placebo-controlled clinical field trial of 122 horses with naturally occurring OA supported by the manufacturer, 1% diclofenac sodium liposomal cream reduced lameness (as judged by owners and veterinarians) regardless of severity or chronicity of the condition. In a SC inflammation model using topically applied 1% diclofenac sodium liposomal cream, the drug was found in transudate at 6 h and significantly decreased carrageenin-induced local production of PGE\textsubscript{2}, showing efficacy. Diclofenac sodium liposomal cream was compared with PBZ and untreated control groups in an osteochondral fragment model to induce OA of the middle carpal joint and was shown to have clinical sign- (clinical improvement in lameness scores) and disease-modifying effects (increased glycosaminoglycan content in articular cartilage and less radial carpal bone sclerosis and cartilage erosion compared with PBZ) in a study supported by the drug manufacturer. In that study, PBZ significantly reduced synovial fluid PGE\textsubscript{2}. However, there were no differences between horses treated with topical 1% diclofenac liposomal cream and controls in lameness score, carpal surface temperature and circumference, synovial fluid cell count, total protein content, and biochemical markers of inflammation in an induced acute synovitis model. Anecdotally, at our hospital, topical application of 1% diclofenac sodium seemed useful in reducing inflammation at regional limb perfusion sites, leading to an investigation supported by the drug manufacturer. In a blinded study of horses undergoing regional limb perfusion, 1% diclofenac liposomal cream significantly reduced local inflammation at perfusion sites, which was judged by visual assessment and ultrasonographic score. This product seems useful in reducing local signs of inflammation.

3. Other Considerations

Individual responses of horses to NSAID administration may be variable, which is similar to responses seen in people; some horses exhibit a more marked response to different NSAIDs than others. What works in one horse may not be efficacious in another horse. Cost is an important factor. At our hospital, cost per day of PBZ (2.2 mg/kg, q 12 h, PO [for tablets; paste formulation is 10 times more expensive]), FM (1.1 mg/kg, q 12 h, PO), and firocoxib (0.1 mg/kg, q 24 h, PO), respectively, are $0.35, $25.00, and $11.00. Given the favorable biological response of most horses to PBZ, I believe that it is still the most cost-effective and efficacious choice. If toxic side effects are noted, a change should be made. Although evidence-based information may equate efficacy of firocoxib and PBZ, my own experience suggests otherwise. Diclofenac sodium seems to have a place as a clinical sign-modifying drug in the management of horses with OA.

References and Footnotes

1. Caron JP. Principles and practices of joint disease treatment. In: Ross MW, Dyson SJ, eds. Diagnosis and man-


