REVIEW

Use of firocoxib for the treatment of equine osteoarthritis

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Abstract: This review presents the pathogenesis and medical treatment of equine osteoarthritis (OA), focusing on firocoxib. Inhibition of prostaglandin E_2 remains a fundamental treatment for decreasing clinical symptoms (ie, pain and lameness) associated with OA in horses. Nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the production of prostaglandin E_2 from the arachidonic acid pathway, continue to be a mainstay for the clinical treatment of OA. Firocoxib is a cyclooxygenase (COX)-2-preferential NSAID that has been shown to be safe and to have a 70% oral bioavailability in the horse. Three clinical reports identified symptom-modifying effects (reduction in pain and/or lameness) in horses with OA administered the once-daily recommended dose (0.1 mg/kg) of oral firocoxib following 7 days of administration. Other reports have suggested that a one-time loading dose (0.3 mg/kg) of firocoxib provides an earlier (1–3 days) onset of action compared to the recommended dose. It is noteworthy that OA disease-modifying effects have been reported in horses for other COX-2-preferential NSAIDs (meloxicam and carprofen), but have not been attributed to firocoxib due to a lack of investigation to date.

Keywords: horse, osteoarthritis, firocoxib, COX-2 inhibitor, NSAID

Introduction

Osteoarthritis (OA) is a common cause of lameness in horses, with the annual national (US) cost of lameness to horse owners estimated to be in the billions of dollars.[1,2] OA, also known as degenerative joint disease, is defined by a group of disorders characterized by articular cartilage deterioration accompanied by changes in the bone and soft tissues of the joint.[3] There are two objectives when treating OA: 1) prevention or inhibition of further articular cartilage, bone, or soft-tissue deterioration, and 2) reduction of clinical symptoms associated with OA. For this reason, pharmaceuticals approved for the treatment of OA are often identified as disease-modifying or symptom-modifying therapies.[4] OA disease-modifying therapies commonly used in the horse include hyaluronic acid, triamcinolone acetonide (corticosteroids), interleukin (IL)-1 receptor-antagonist protein, polysulfated glycosaminoglycans (GAGs), diclofenac, avocado and soybean unsaponifiable extracts, and surgical intervention.[5–11] Common symptom-modifying therapies include corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and potentially hyaluronic acid.[6,10,12–15]

NSAIDs inhibit components of the enzyme system that converts arachidonic acid into prostaglandins (PGs) and thromboxanes (Figure 1). PGs, primarily PGE_2, have been associated with inflamed joints and degradation of the articular matrix, and inhibition of PGE_2 has been a mainstay of OA treatment in the horse for decades.[16] Firocoxib (Equioxx®; Merial, Duluth, GA, USA) is an NSAID, more specifically a cyclooxygenase (COX)

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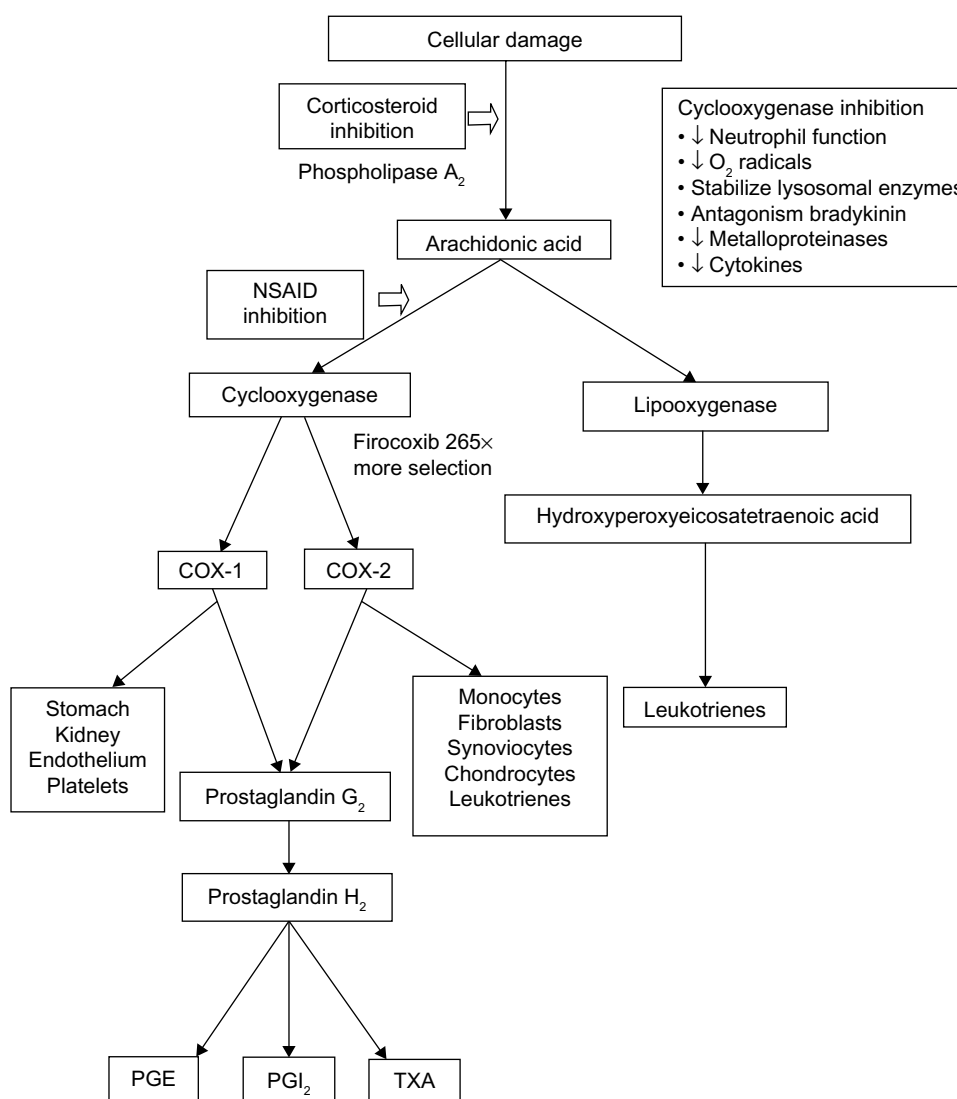Fax +1 970 297 4138
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Figure 1 Schematic representation of inhibition of the inflammatory cascade by nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid.
Abbreviations: COX, cyclooxygenase; PG, prostaglandin; TXA, Thromboxane A2.

inhibitor, which is highly specific for the COX-2 isoenzyme.[17,18] Firocoxib is approved for the control of pain and inflammation associated with OA for up to 14 days. Firocoxib in a paste form (also available in injectable form) has become a commonly prescribed treatment of clinicians for long-term treatment of OA, and more specifically chronic OA.

This review presents the pathogenesis and medical treatment of OA with firocoxib compared to other NSAIDs in the horse. Pharmacodynamics, pharmacokinetics, and safety of firocoxib in the horse are also reviewed.

Osteoarthritis
Pathogenesis

Articular cartilage damage (OA) commonly occurs due to abnormal forces on healthy cartilage caused by instability or traumatic disruption of the soft tissue-supporting structures of the joint or typical forces on abnormal cartilage.[19] The force, lack of stability, and acute trauma typically cause synovitis and capsulitis of the joint.[20] Inflammation within the joint can cause OA even in the absence of direct forces on the cartilage, due to the release of enzymes, inflammatory mediators, and cytokines.[21,22] Current enzymes, inflammatory mediators, and cytokines considered to be noteworthy in the horse include matrix metalloproteinases (MMPs; aggrecanases, collagenase, gelatinases, and stromelysins), free radicals, IL-1, tumor-necrosis factor (TNF)-α, and PGs (primarily PGE_2).[19] These have been shown to directly or indirectly cause degradation of the normal articular cartilage matrix, which primarily includes type II collagen, and proteoglycans, formed by a protein core and GAG side chains.

Notable GAGs of interest in equine adult cartilage are chondroitin-6 sulfate and keratin sulfate.

MMPs, free radicals, IL-1, TNFα, and PGE_2 can be released into synovial fluid by synoviocytes and/or chondrocytes. The most notable MMPs in the horse are MMP-2, -3, -9, and -13. They are activated by proteinases within the synovial fluid, and cause breakdown of type II collagen and proteoglycans. Free radicals have been shown to increase in equine joint disease, with evidence supporting free radicals' ability to cleave proteoglycans and degrade collagen.[23,24] Cytokines, such as IL-1 and TNFα, may be produced by synoviocytes, chondrocytes, and subchondral bone, and can modulate the synthesis of MMPs and PGE_2 by both synoviocytes and chondrocytes. These cytokines cause proteoglycan depletion within articular cartilage by increasing the rate of degradation or decreasing synthesis in association with the release of proteinases and PGE_2 from chondrocytes.

PGE_2 is produced and released by synoviocytes and chondrocytes (stimulated by cytokines) as the result of acute trauma to the joint. Levels of PGE_2 are commonly used as an objective measure of the amount of inflammation within the joint, because they are associated with synovial inflammation in horses with OA and cartilage-matrix depletion.[25–28] PGE_2 is associated with vasodilation, enhancement of pain perception, proteoglycan depletion of cartilage, bone demineralization, and promotion of plasminogen activation secretion.[29] Elevation of PGE_2 within joint tissues is historically thought to correlate with clinical signs associated with OA. More recently, the effects of PGE_2 within the joint were complicated by a study that reported that exogenous PGE_2 significantly reduced IL-1β-induced expression of MMP-1, -3, and -13 and tissue inhibitor of MMP-1.[30] The authors concluded that the potential for physiologically relevant regulation of expression of these genes by PGE_2 is a consideration when considering drugs that inhibit prostanoid synthesis in the treatment of equine arthropathies.[30] The authors also mentioned that while certain studies suggest a catabolic effect of PG in joints, other data suggest the E-series PGs are protective of cartilage-matrix synthesis.[31] The authors also noted these findings were similar to DiBattista et al,[32] who showed that progressively higher doses of PGE_2 essentially eliminated MMP-1 expression by synovial fibroblasts, but similar concentrations of prostanoids were only capable of reducing stromelysin expression to a certain level, after which it was uninfluenced by further increases in dose. While these results challenge some of the long-held beliefs regarding the role of PGE_2, the importance of this molecule in OA remains.

Clinical signs of OA

Clinical signs of equine OA include lameness, decreased range of motion, heat, crepitus, and effusion within a joint. Lameness is the most common clinical sign of OA, with a poor correlation between the extent of radiographic OA and the degree of lameness.[33–36] Lameness occurs as a result of pain (a symptom) or mechanical restriction of the joint due to chronic fibrosis on soft tissue.[37] Pain associated with OA has been recently reviewed, and readers are redirected to van Weeren and de Grauw[38] for current research. Inhibition of PGE_2 for the symptomatic relief of lameness associated with OA has traditionally been and is currently viewed as a beneficial goal in reducing clinical signs associated with OA.[16,39] Although treatment of OA with NSAIDs is controversial due to the limited reports for their disease-modifying effects on OA, they are still a mainstay in clinical practice.[40]

Firocoxib
Pharmacodynamics

NSAIDs are anti-inflammatory agents that inhibit the conversion of arachidonic acid into PGs and thromboxane via inhibition of COX activity. This differs from corticosteroids, which inhibit synthesis of arachidonic acid via phospholipase A_2, which inhibits both COX and lipoxygenase activity (Figure 1). Further identification of isoenzymes (COX-1 and -2) within the arachidonic acid pathway have provided more specific therapeutic targets. While all NSAIDs inhibit both COX-1 and -2 to some degree, NSAIDs are commonly classified as inhibiting both COX-1 and -2 (COX-nonpreferential, ie, phenylbutazone and flunixin meglumine) or inhibiting COX-2 (ie, firocoxib and meloxicam).[25] COX-1 is known to be constitutively produced and important in housekeeping functions, having a protective role in the balance of normal physiologic function of the gastrointestinal and renal systems and a lesser role in the inflammatory cascade.[16] COX-2 has mainly been associated with the inflammatory cascade driven by macrophages and synovial cells, and having only a minor role in normal physiological function. Therefore, the analogy of COX-1 being the good COX and COX-2 being the bad COX has developed. While in principle the analogy is good, it is not wholly accurate, as overlap between both COX-1 and -2 does exist (Figure 1).

A crossover-design study was performed to test the efficacy of firocoxib on COX inhibition.[41] This study included eight (four per group) adult horses administered 57 mg of paste (Equioxx) or tablet (Previcox®; Merial) formulations of firocoxib for 14 days and ten untreated control horses. Blood was collected 1 hour before dosing on days 0 and 7,

and 1 hour after day 7 dosing from each horse. A decrease in COX activity in the firocoxib-treated group was determined by a decrease in PGE_2 concentration within samples stimulated with lipopolysaccharide (LPS), which has been shown to increase PGE_2 levels in blood, compared to untreated samples. The authors reported that 57 mg of the tablet and paste form inhibited PGE_2 within the blood of treated horses compared to blood in untreated horses.[41] Another ex vivo study assessed the efficacy of phenylbutazone, flunixin meglumine, and firocoxib on COX activity in 18 horses undergoing elective surgery.[42] The recommended dose of each NSAID was administered intravenously (IV) depending on clinician preference (number of horses in each group unknown), and residual blood samples were collected prior to and 2 and 4 hours following surgery. Results of the study showed a significantly greater activity of the COX-1 isoenzyme in horses receiving firocoxib compared with horses receiving phenylbutazone or flunixin meglumine. COX-1 activity was reduced (compared to baseline) in horses receiving phenylbutazone and flunixin meglumine, and the effect of COX-2 activity was not significantly different between all three drugs. The authors concluded that firocoxib preserved the physiological action of COX-1 isoenzyme, but was as effective as phenylbutazone and flunixin meglumine in modulating the production of PGs by the COX-2 isoenzyme in blood.[42] This report did not quantify the selectivity of firocoxib on COX-2 relative to COX-1, but other authors have reported that firocoxib is approximately 265 times more selective in inhibiting COX-2 relative to COX-1.[43]

Pharmacokinetics of firocoxib in the horse

The pharmacokinetics of oral and IV administration of firocoxib have been described in multiple single-dose and multiple consecutive-dose concentrations in horses.[44–47] Administration of a single oral dose of firocoxib at 0.1 mg/kg (recommended dose) had average bioavailability (79%), with a maximum plasma concentration of 75±33 ng/mL at 4 hours and an elimination half-life of 30±7.5 hours.[47] Maximum concentration of IV administration of the same dose was 210±0.05 ng/mL, with an elimination half-life of 34±11 hours.[47] More recently, in a balanced three-way crossover study, nine (three per group) healthy adult horses were administered the oral paste form of firocoxib at 0.1 mg/kg once a day (semel in die [SID]) for 14 days, a tablet form at 57 mg SID for 14 days, or the IV form at 0.9 mg/kg SID for 5 days.[46] The mean steady-state concentration of plasma half-life (1.7±0.8, 1.7±0.8, 1.6±0.7 days) and time to last

detected plasma concentration (29.3±8.4, 29.1±7.4, and 20.7±3.2 ng/mL) was similar for paste, tablet, and injectable formulations, respectively.[46] In the same study, the mean steady-state plasma concentration was 94.9±28.3 ng/mL and 112±40.3 ng/mL, and the maximum concentration after the last dose was 118±40.5 ng/mL and 137±47.7 ng/mL for the oral paste and tablet form, respectively. These results indicate that when used at the recommended dose, all three formulations of firocoxib are similar in distribution and clearance. As of April 2014, when used at the recommended dose, all three formulations fell below the US Equestrian Federation (USEF) 2014 threshold (240 ng/mL) for the entire sampling period in all horses, and below the Racing Medication and Testing Consortium threshold (20 ng/mL) in all horses 7 days after administration of the final dose.[48,49]

A similar study has been performed with six healthy adult horses administered 0.1 mg/kg oral paste firocoxib for 12 consecutive days and 12 healthy adult horses administered 0.2 mg/kg IV firocoxib for 9 consecutive days.[50] In this study, the mean steady-state plasma concentration was 130±36 ng/mL and 229±73 ng/mL for the oral paste and tablet form, respectively, and the maximum concentration after the last oral dose was 173±44 ng/mL. These two studies are compared to a study administering six healthy adult horses 0.3 mg/kg oral paste on day 1 (as a loading dose) and nine consecutive doses of 0.1 mg/kg (as a maintenance dose) every 24 hours. The mean steady-state plasma concentration was 150±45 ng/mL, and maximum concentration after the last dose was 199±97 ng/mL.[44] The authors of this study stated that "The main advantage of including a loading dose is the achievement of near steady-state concentrations after the first day of treatment rather than 7 days after the initiation of the therapy".[44]

The long terminal half-life of firocoxib in the horse is most likely a result of a large volume of distribution and relatively low total-body clearance.[44] Compared to phenylbutazone, ketoprofen, and flunixin meglumine, firocoxib has a five to 30 times longer terminal half-life.[51] This is an indication that firocoxib has a longer duration of action once it reaches a steady-state concentration compared to other NSAIDs. With reports identifying the time to steady-state concentration of firocoxib (dose 0.1 mg/kg) being 7 days, the onset of action may be prolonged compared to other commonly used NSAIDs for the treatment of OA in the horse. Incorporating a loading dose (0.3 mg/kg) of firocoxib may decrease the time of onset of action compared to other NSAIDs, and appears to be below the allowed threshold for USEF competitions, although the clinical benefit of this is unknown.

Safety of firocoxib

There has been a very low incidence of reported adverse effects for oral and IV administration of firocoxib when administered alone at the recommended dose (0.1 mg/kg for up to 42 days).[15,45,52] Adverse effects, such as edema of the lips, minor episodes of colic, mild oral ulcerations, lethargy, and sedation,[53] in four of 476 (0.9%) horses, and labial and tongue edema and hypersalivation in one of 48 (2%) horses[54] have been reported when administering oral paste firocoxib at the recommended dose. A study administering six horses both firocoxib (0.1 mg/kg) and phenylbutazone (4.4 mg/kg) for 10 days reported an increase in creatinine and total protein supportive of renal disease at day 10.[55] This study assessed changes in serum creatinine, albumin, total protein, and urine-specific gravity prior to firocoxib and phenylbutazone administration, then again at day 10. The study also assessed daily behavior changes, appetite, fecal consistency, signs of abdominal pain, and oral mucous ulceration. Target animal-safety studies report oral ulceration in horses administered firocoxib oral paste at three and five times the recommended dose for 42 days and clinical chemistry and coagulation abnormalities in horses administered five times the recommended dose for 42 days.[52] A follow-up study reported delayed healing of preexisting oral ulcerations in all horses and renal papillary necrosis in one of eight horses administered firocoxib oral paste at the recommended dose. IV administration of firocoxib has been associated with injection-site swelling and perivascular inflammation in horses administered one to five times the recommended dose.[56] With relatively low adverse effects, the use of firocoxib is safe when administered at the recommended doses. With no reports of gastric ulceration as an adverse effect after prolonged administration, there is a common clinical perception that firocoxib is a safe alternative to nonpreferential NSAIDs, especially in horses that are diagnosed or presumed to have gastric ulceration.

COX-1 has been shown to be protective to gastroduodenal mucosa in laboratory animals and humans, and the greatest degree of damage to gastroduodenal mucosa is generally caused by NSAIDs that preferentially inhibit COX-1.[57] Because of the potential for nonpreferential NSAIDs to cause gastric ulceration, it is currently thought that the use of COX-2-preferential NSAIDs is a safe alternative to nonpreferential NSAIDs in horses. A placebo-controlled study identified the effect of phenylbutazone on the gene expression of *COX1* and *COX2* in the oral, glandular, gastric, and bladder mucosa of 12 healthy horses.[58] Horses were allocated equally to receive 4.4 mg/kg of phenylbutazone or placebo treatment twice daily for 7 days. Oral glandular gastric and urinary mucosa biopsies were collected transendoscopically before and after the treatment period. *COX1* and *COX2* gene expressions were determined and compared in samples before and after treatment. The authors reported that the *COX1* gene was expressed in all tissues, and the *COX2* gene was expressed in all tissue except the oral mucosa. The authors concluded that administration of phenylbutazone at the maximum recommended dose for 7 days did not affect *COX1* or *COX2* gene expression in oral, glandular, gastric, or bladder mucosa.[58] Other authors have reported that firocoxib may be advantageous compared to flunixin meglumine in horses recovering from gastrointestinal injury.[59] Gastric ulceration has been reported as an adverse effect of phenylbutazone in ponies and adult horses at greater than two times the recommended dose.[60,61] Without reports identifying gastric ulceration as an adverse effect of nonpreferential NSAIDs when used at the recommended dose, COX-2-preferential NSAIDs are most likely not safe any more when compared to phenylbutazone or flunixin meglumine, except when the gastric mucosa is already compromised.

Effect of firocoxib on OA

To date, there have not been any reports identifying disease-modifying effects of firocoxib in equine OA, only symptom-modifying effects. Sixty-four horses with lameness, of which 33 were presumed to be due to OA and 31 due to navicular syndrome, were evaluated for lameness using the American Association of Equine Practitioners (AAEP) 0–5 lameness scale and force-plate measurement prior to oral paste firocoxib administration and on days 0 (first day of administration), 2, and 6.[62] Horses were randomly allocated into one of three treatment groups or a control group. Horses in the treatment groups were administered firocoxib oral paste at a dose of 0.05 mg/kg, 0.02 mg/kg, or 0.25 mg/kg every 24 hours for 7 days. Baseline force-plate analysis was performed, and subsequent force-plate analyses were performed on days 0, 2, and 6, and at 10 hours posttreatment. The authors reported a significant increase in peak vertical force (indicating horses were less lame) on day 6 in horses receiving 0.5 mg/kg, days 2 and 6 in horses receiving 0.01 mg/kg, and days 0, 2, and 6 in horses receiving 0.25 mg/kg. Significant decreases in lameness scores from baseline in all treatment groups and control horses with time were identified as well. The authors of this report concluded that force-plate analysis objectively identified that 0.1 mg/kg was an effective dose of firocoxib to decrease chronic lameness.[62] This report grouped horses with OA and horses with radiographic signs

of navicular disease together, and did not specify if horses with OA differed in their response to treatment compared to the horses with navicular disease. Navicular disease and OA have different etiologies, but the decrease in lameness (pain) associated with both diseases is likely similar and clinically beneficial.

A more recent study evaluated improvement in lameness in 390 of 429 horses from 80 sites and 20 states with musculoskeletal pain and lameness associated with OA.[53] Signs of musculoskeletal pain or lameness attributed to OA were diagnosed in a single joint in 197 of 360 (50.5%) horses and in multiple joints in 193 of 390 (49.5%) horses. Clinicians and horse owners or handlers assessed improvement in lameness at 7 and 14 days posttreatment with oral paste firocoxib (0.1 mg/kg) for 14 days. Clinicians reported improvement in 79%, and owners or handlers reported improvement in 85% of horses at the end of the study with the most rapid improvement being within 7 days after starting treatment. The authors concluded that firocoxib was a safe treatment for musculoskeletal pain and lameness in horses with OA, with only four of 467 horses (0.9%) having adverse effects, which included edema of lips and gums, mild episodes of colic, and mild oral ulcers.[53] Without a control group in this study, there was likely a very high bias for veterinarians and owners to identify the horses as improved because they knew the horse was receiving a treatment, which is comparable to the control horses improving on clinical evaluations in the first study identified. This is an indication that more controlled studies with objective measures are needed to truly assess firocoxib's effect on lameness.

Effect of firocoxib on OA compared to other NSAIDs

The oral paste form of firocoxib has been compared to many NSAIDs for the treatment of lameness in horses.[15,54] Phenylbutazone is the most commonly used NSAID in horses, based on efficacy, availability, and affordability. It can be given orally or IV, and is relatively nontoxic at repeated doses of 2.2 mg/kg twice daily or less.[63] The effects of phenylbutazone on OA vary both in horses with naturally occurring OA[64] and in experimental trials using an equine OA model.[8] In a crossover-design study with 28 horses, objective lameness scores were significantly lower ($P<0.05$), but never reached the threshold for being sound, after administration of the combination of phenylbutazone (2.2 mg/kg) with flunixin meglumine (1.1 mg/kg, for 5 days) compared with phenylbutazone alone (2.2 mg/kg for 5 days).[64] A clinically subjective improvement was seen in 23 of 28 (82%) horses, and secondary side effects (including acute necrotizing

colitis; one of 28 horses) were raised in horses receiving both phenylbutazone and flunixin meglumine.

A randomized controlled clinical trial with 253 horses with naturally occurring OA, including navicular disease, compared the efficacy and safety of paste formulations of firocoxib and phenylbutazone.[15] All horses were treated with either firocoxib (0.1 mg/kg PO, q 24 hr) or phenylbutazone (4.4 mg/kg PO, q 24 hr) for 14 days. Physical exam and lameness evaluations were performed prior to treatment and on days 7 and 14. Improvement in lameness was defined as a decrease in lameness of at least 1 grade (AAEP lameness scale) or a combination of at least 3 points in scores for pain during manipulation or palpation, joint swelling, joint circumference, and range of motion. There was no significant difference in the overall percentage of horses that improved in clinical lameness scores between the phenylbutazone (87%)- and firocoxib (85%)-treated horses. The overall percentage of horses that improved were significantly higher for pain on manipulation or palpation ($P=0.028$, 75% versus 50%), joint-circumference score ($P=0.026$, 35% versus 13%), and range-of-motion score ($P=0.012$, 45% versus 30%) in the firocoxib-treated horses compared to the phenylbutazone-treated horses. The authors concluded that the paste formulation of firocoxib was safe (health and behavioral abnormalities seen in only three of 123 [2.4%] of the firocoxib-treated horses and four of 119 [3.4%] of the phenylbutazone-treated horses), and that overall clinical efficacy was comparable to phenylbutazone.[15] In summary, phenylbutazone and firocoxib appear to have a similar effect on clinical improvement in lameness for horses with naturally occurring OA and navicular disease 7 and 14 days after administration, with firocoxib potentially having a greater clinical improvement than phenylbutazone for focal pain, joint effusion, and range of motion, at least when administered for 14 days.

Another less commonly used NSAID for the treatment of lameness associated with OA in the adult horse is ketoprofen. Synovial fluid concentrations of ketoprofen have been shown to be 6.5 times higher in joints with induced synovitis than in healthy control joints when administered 2.2 mg/kg IV.[65] Ketoprofen was compared to phenylbutazone in a randomized controlled study with 24 horses (six horses per group) with induced synovitis of an intercarpal joint.[66] Horses were pretreated (ie, before induction of synovitis) with ketoprofen at a 2.2 mg/kg dose or 3.62 mg/kg dose IV phenylbutazone (4.4 mg/kg IV) or saline solution (control). Clinical assessments and synovial fluid analysis were performed at multiple time points up to 48 hours postinduction. The authors concluded that phenylbutazone was more effective

than ketoprofen in reducing lameness, joint temperature, synovial fluid volume, and synovial fluid PGE_2.[66]

Although comparisons have not been made between firocoxib and ketoprofen, a randomized, controlled, doubled-blinded, multicenter field trial compared firocoxib to vedaprofen, which is available in a paste formulation in the UK, Europe, and Canada.[54] Vedaprofen and ketoprofen are both classified as propionic acid NSAIDs, but differ in that vedaprofen appears to have more of an affinity for COX-1 rather than COX-2 and is bioavailable orally, whereas ketoprofen is not.[38] In this field trial, 96 horses with a lameness score of at least 3 or grade 2 (AAEP lameness scale) plus a score of at least 2 for either pain on palpation, range of motion, or joint swelling were analyzed.[54] Horses were divided into two equal treatment groups, with one group receiving oral paste firocoxib (0.1 mg/kg q 24 hr), or a single loading dose (2 mg/kg) then twice-daily dose (1 mg/kg) of oral paste vedaprofen, each for 14 days. Physical exams and lameness evaluations were performed prior to treatment and on days 7 and 14. Although no significant differences were found between the two treatment groups, 83% of the horses treated with firocoxib showed clinical improvement compared to 65% of the horses treated with vedaprofen at the 14-day time point. The authors concluded that the oral paste form of firocoxib was highly effective, well tolerated, and acceptable for the control of pain and inflammation associated with lameness in horses.[54]

Other preferential COX-2 NSAIDs used in the horse

Meloxicam and carprofen, although used more frequently in dogs than horses, are occasionally prescribed in horses for symptomatic treatment of OA. Both meloxicam and carprofen have been shown to inhibit COX-2 in equine blood more selectively than phenylbutazone, and flunixin meglumine at half-maximal inhibitory concentration (IC_{50}).[67] However, phenylbutazone and flunixin had greater COX-2 selectivity at IC_{80} than at IC_{50}, and meloxicam and carprofen had lower COX-2 selectivity at IC_{80} than at IC_{50}. Other authors have questioned the inhibition of COX by carprofen in horses.[68] This is an indication that IC_{80} rather than IC_{50} should be used when evaluating COX-inhibition NSAIDs, and the classification of meloxicam and carprofen as COX-2-preferential NSAIDs in horses is questionable.

The pharmacokinetics and safety of oral meloxicam, more commonly used in foals than adult horses, have been reported. At a dose rate of 0.6 mg/kg, the mean plasma half-life appears to be to be relatively short for foals[69]

(2.48±0.25 hours) and adult horses[70] (4.99±1.11 hours). Although the authors reported that there was no significant increase in gastric ulceration compared to the start of the study, they reported an increase in gastric ulceration in four of 16 (25%) horses, and one of 16 (6%) horses developed a severe hypersensitivity reaction (day 8) at an oral dose of 0.6 mg/kg for 14 days.[70] While controversy still exists whether meloxicam preferentially inhibits COX-2 or if COX-2 therapies are safer than nonpreferential NSAIDs, meloxicam does not appear to be protective against gastric ulceration. Although the mechanism of action and gastrointestinal protection of meloxicam is questionable, there is supportive evidence in dogs and limited supportive evidence in horses of its OA disease- and symptom-modifying effects.[71,72]

A crossover placebo-controlled study identified the effects of meloxicam on biomarkers of inflammation, MMP activity, and cartilage biomarkers in six horses with induced synovitis due to intra-articular (intercarpal) administration of 0.5 ng of LPS after receiving oral meloxicam (0.6 mg/kg) once daily for 1 week.[73] Lameness (P=0.026), joint effusion (P=0.059), and carpal circumference (P=0.052) decreased in the meloxicam-treated horses at 8 and 24 hours after administration of LPS compared to placebo-treated horses, with lameness resolving by 48 hours in all horses. Meloxicam-treated horses had significantly lower general MMP activity (P=0.013 [8 hours] and P=0.05 [24 hours]), GAG concentration (P=0.008 [24 hours]), and type II collagenase cleavage fragment (P<0.001) and type II collagen carboxypropeptide (P<0.004) concentrations compared to placebo-treated horses. PGE_2 (P<0.001), substance P (P<0.001), and bradykinin (P=0.08) levels were suppressed compared to placebo-treated horses at the 8-hour time point. The authors concluded that meloxicam suppresses acute transient synovitis and may limit inflammation-induced cartilage metabolism, suggesting disease-modifying effects.[73] Similar disease-modifying effects have been shown with carprofen.

The pharmacokinetics of oral and intramuscular formulations of a 0.7 mg/kg dose of carprofen given for 14 days identified a plasma half-life of 21.9±2.3 hours, with the authors reporting elevated levels of plasma creatinine kinase (suggestive of muscle-cell damage) in horses that were administered the intramuscular formulation.[74] Anecdotally, carprofen has been used at Colorado State University in horses that developed high serum creatinine levels and diarrhea in association with phenylbutazone use. These side effects disappeared after discontinuation of phenylbutazone with carprofen administration. It was implied

that there may be more preferential COX-2 inhibition than with phenylbutazone therapy.

There are reports that carprofen may delay the progression of OA and have symptom-modifying effects in the dog, but reports on the horse are limited.[72,75] One study compared the release of inflammatory proteins within equine cartilage explants treated with nothing (control), IL-1β (10 ng/mL), carprofen (100 μg/mL), and carprofen (100 μg/mL) and IL-1β (10 ng/mL).[76] The authors reported that carprofen significantly decreased MMP release and the appearance of a 60 kDa fragment of fibronectin 1 without causing detectable cytotoxicity to chondrocytes. The authors concluded that carprofen exhibited beneficial anti-inflammatory and anticatabolic effects on equine cartilage in vitro.[76] Although in vivo disease-modifying effects of OA have been shown when administering carprofen in the horse, the drug continues to be rarely used, due to its adverse effects (high serum creatinine levels), questions as to its inhibition of COX, and lack of clinical data.

Conclusion

Inhibition of PGE_2 remains a fundamental treatment for decreasing clinical signs (ie, pain and lameness) associated with OA in horses. The inhibition of PGE_2 by NSAIDs classifies them as symptom-modifying drugs, with little-to-no support that they have a disease-modifying effect. The COX-2-preferential NSAID firocoxib has been shown to be safe, have average bioavailability orally, have a large volume of distribution, and cause a reduction in lameness at the recommended dose in horses.

Current clinical reports suggest that when using firocoxib (paste, tablet, or injectable form) at the recommended dose (0.1 mg/kg), a clinical improvement is seen in at least 7 days and is comparable to phenylbutazone alone at this time period. One report has documented an objective improvement in lameness at the recommended dose as early as 2 days and as early as 10 hours with a 0.25 mg/kg dose. In the authors' opinion, when administered at the recommended dose, firocoxib has a longer onset of action (assessed by clinical improvement in lameness) compared to phenylbutazone. This may be explained by the increased duration for time to steady-state concentration at the recommended dose, which is routinely recommended by the authors. Administration of a loading dose (0.3 mg/kg) could potentially produce an earlier clinical improvement, similar to that seen with phenylbutazone, when administering firocoxib.

Firocoxib continues to be a noteworthy and well-accepted treatment for reducing clinical signs associated with OA in the horse. With promising disease-modifying effects of other therapeutics, described as COX-2-preferential NSAIDs (meloxicam and carprofen), further controlled studies are needed to evaluate the disease-modifying potential of firocoxib on OA.

Disclosure

None of the authors has a financial interest or a personal relationship with other people or organizations that could inappropriately influence or bias the content of this review article.

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