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NARRATIVE REVIEW

Non-steroidal anti-inflammatory drugs in equine orthopaedics

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Summary

Orthopaedic disorders are commonly encountered in equine veterinary medicine, and non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the management of many equine orthopaedic disorders. There are multiple NSAIDs available for use in horses, including both non-selective and selective NSAIDS, and the body of literature evaluating the efficacy of these medications, their effects on normal and inflamed musculoskeletal tissues, and their side effects is broad. This review aims to summarise the current literature on the use of NSAIDs for equine orthopaedic disorders and examines new and future avenues for the management of inflammation in equine orthopaedics.

KEYWORDS
horse, non-steroidal anti-inflammatory drug, orthopaedics, osteoarthritis

1 | INTRODUCTION: ROLE OF NSAIDS IN MANAGEMENT OF ORTHOPAEDIC PAIN

Orthopaedic disorders are one of the most common complaints that will be managed by the equine practitioner and one which plays a significant role in the loss of use and wastage of horses within multiple equine disciplines.[1-5] Orthopaedic disease can be acute or chronic, is accompanied by inflammation and often manifests as lameness.

Following injury or disruption to one or multiple musculoskeletal tissues, the inflammatory cascade is activated, leading to local increased recruitment of proinflammatory cells that release an array of cytokines and prostanoids. Production of prostanoids, importantly prostaglandin E2 (PGE2), through metabolism of arachidonic acid by cyclooxygenase (COX), is an important component of the inflammatory reaction. Prostanoids contribute to pain and hyperalgesia by increasing the sensitivity for signalling by peripheral nociceptive terminals.[6] Tissue injury also stimulates release of neurotransmitters from central terminals of nociceptors and augments production of PGE2 in the spinal cord. This leads to additional excitation and disinhibition of dorsal horn neurons and generates abnormal responses to sensory signals from the periphery.[7]

One of the main goals in management of orthopaedic disease in horses is reduction of inflammation and, as a result, reduction in associated pain and lameness. Another goal is to minimise disease progression and long-term deterioration of tissues.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most readily available and cost-effective methods to inhibit the inflammatory response and, as a result, these drugs continue to be a mainstay of management of equine orthopaedic injury and lameness. In cases of acute orthopaedic disease, such as septic arthritis, NSAIDs are important in blunting the initial inflammatory response in order to decrease pain and to prevent further propagation of inflammation. These drugs also play important roles in modulating chronic disease, such as that seen with osteoarthritis (OA), by controlling persistent inflammation and slowing the progression of disease. Clinicians need to be cognisant of the potential gastrointestinal and renal side effects associated with the administration of NSAIDs. Gastrointestinal effects include oral and gastric ulceration and right

dorsal colitis while renal papillary necrosis occurs secondary to decreased perfusion to the renal medulla.[8] With injectable forms of NSAIDs, intra-arterial injection such as an intra-carotid injection can cause central nervous system stimulation and potentially seizures.[9]

Both systemically administered and topically applied NSAIDs are used in horses for management of lameness and are often subdivided into non-selective COX inhibitors and selective COX-2 inhibitors.

Phenylbutazone and flunixin meglumine, both non-selective COX inhibitors, are the two most commonly prescribed NSAIDs in equine medicine in the United States, the United Kingdom and Canada.[10] In cases of orthopaedic pain, phenylbutazone is reported to be the most commonly prescribed NSAID, followed by flunixin meglumine.[10] Phenylbutazone is more cost effective and has been available for a longer period compared with flunixin meglumine, which likely promotes its increased use among horses with lameness and orthopaedic problems. Common clinical dosing of phenylbutazone is 2.2-4.4 mg/kg every 12-24 hours. Doses that do not exceed 2.2 mg/kg twice daily were found to be relatively safe, but the duration of dosing at 4.4 mg/kg twice daily should be minimised to decrease the risk of toxic effects to the gastrointestinal and renal systems.[11-14] In horses with navicular syndrome, a higher phenylbutazone dose (8.8 mg/kg) administered intravenously once daily had similar analgesic effects when compared with a lower dose (4.4 mg/kg).[15] Phenylbutazone can be administered intravenously or orally; however, intramuscular and subcutaneous injection are not recommended as swelling, necrosis and sloughing of tissue can occur.[9]

Studies have found phenylbutazone to be effective in alleviating experimentally induced acute lameness and naturally occurring chronic lameness.[14,16] Raekallio et al also found phenylbutazone to lower the total postoperative pain severity index in horses following arthroscopic surgery when compared with a saline control.[17] In horses with experimentally induced middle carpal joint OA, long-term administration of phenylbutazone (4.4 mg/kg) was shown to cause increased bone sclerosis and higher scores for cartilage erosion when compared with horses receiving topical diclofenac, which may provide some evidence against chronic administration of phenylbutazone in OA cases.[18]

Flunixin meglumine is available as a solution for intravenous injection or as a preparation for oral dosing. Flunixin meglumine is labelled for administration at 1.1 mg/kg given once daily; however, clinically it is often administered at this dose every 12-24 hours. Injectable flunixin meglumine is labelled for intravenous or intramuscular injection; however, intramuscular administration should be avoided due to the risk of development of clostridial myonecrosis.[19-20] Recently, a study has evaluated the pharmacokinetics of a bovine transdermal formulation of flunixin meglumine in horses.[21] In this study, transdermal administration (500 mg) was well tolerated in horses with no adverse effects noted. The maximum systemic concentration of flunixin meglumine was lower and the time to maximum absorption was longer than reported for oral and intramuscular administration; however, inhibition of COX-1 and COX-2 was identified for 24-72 hours post administration.[21]

Although phenylbutazone is more commonly used in cases of orthopaedic pain and disease, flunixin meglumine is also effective in decreasing lameness. A study examining doses of flunixin meglumine at 0.5, 1.1 and 2.2 mg/kg in horses with experimentally induced lameness found decreases in heart rate and lameness scores with all treatment groups. The higher doses (1.1 and 2.2 mg/kg) of flunixin meglumine reduced heart rate and lameness for a longer period of time compared with the 0.5 mg/kg dose; however, there was no significant difference between the 1.1 and 2.2 mg/kg doses.[22] Because no additional benefits were identified with the 2.2 mg/kg dosing and due to the concerns for an increased risk of side effects, the 2.2 mg/kg dosing of flunixin meglumine is not commonly recommended or used clinically.

Studies comparing phenylbutazone and flunixin meglumine have discovered little difference in their effectiveness for treating lameness. Foreman and colleagues found a single dose of either phenylbutazone (4.4 mg/kg, IV) or flunixin meglumine (1.1 mg/kg, IV) to relieve experimentally induced foot lameness to a similar degree before, during and after exercise on a treadmill.[23] This group also found administration of a combination of phenylbutazone (4.4 mg/kg, IV), and flunixin meglumine (1.1 mg/kg, IV) was not more effective than administration of phenylbutazone or flunixin meglumine separately in experimentally induced foot lameness.[24] A significant improvement in subjective lameness scores and peak vertical force was observed in horses with navicular syndrome treated daily for 4 days with clinical doses of either phenylbutazone (4.4 mg/kg, IV) or flunixin meglumine (1.1 mg/kg, IV) with both drugs improving lameness to a similar degree.[25] Some studies have found combinations of phenylbutazone and flunixin meglumine to have increased analgesic capabilities and prolonged anti-inflammatory effects.[26,27] The potential to achieve greater improvement in lameness with administration of multiple NSAIDs has led to 'stacking' of these medications not only in competition and racing horses but also in horses being treated for severe orthopaedic disorders, such as laminitis. The use of any NSAID prior to competition is inappropriate due to the potential to mask lameness which puts competition and racing horses at risk of catastrophic injuries and detrimental side effects. As a result, gaming commissions and the United States Equestrian Federation (USEF) have restrictions on the timing of NSAID administration allowed prior to racing or competition. The practice of administering multiple NSAIDs concurrently is also unethical and has led to 'NSAID Anti-Stacking' rules by gaming commissions and the USEF. Current USEF rules state that whenever two NSAIDs are administered, by any route, one must be discontinued at least 3 days prior to competition.[28]

A study evaluating postoperative analgesia, with a majority of horses undergoing arthroscopic surgery, found no difference in postoperative pain scores or in the number of horses requiring additional analgesia between horses receiving intravenous phenylbutazone (4 mg/kg), flunixin meglumine (1 mg/kg) or carprofen (0.7 mg/kg).[29] It was noted, however, that of horses that required additional analgesia following surgery, those that received flunixin meglumine had a longer interval (12.8 hours) after surgery before additional

analgesia was administered compared with horses receiving phenylbutazone (8.4 hours).

In summary, phenylbutazone and flunixin meglumine are both commonly used non-selective NSAIDs in equine practice. For most equine orthopaedic disorders, recommended clinical dosing of phenylbutazone is 2.2 mg/kg every 12 hours or 4.4 mg/kg 24 hours and recommended clinical dosing of flunixin meglumine is 1.1 mg/kg every 12 hours. Both medications are available in oral and intravenous formulations. Phenylbutazone is less expensive, but both medications have similar effectiveness at reducing experimentally induced and naturally occurring lameness. Flunixin meglumine has been shown to provide a longer time of analgesia following arthroscopic surgery compared with phenylbutazone.

Firocoxib is a COX-2-selective NSAID that is approved by the US Food and Drug Administration for the management of musculoskeletal pain and lameness associated with OA in horses. Firocoxib is available as an intravenous injection and as an oral paste or tablet. The labelled dosing for injectable firocoxib is 0.09 mg/kg once daily for up to 5 days. Dosing for the oral paste or tablets is 0.1 mg/kg once daily for up to 14 days. Administration at the labelled dose requires 5-7 days of administration to reach a plateau or steady-state plasma firocoxib concentration.[30] A recent study has found administration of oral firocoxib at a loading dose of 0.3 mg/kg resulted in the maximum drug concentration in plasma being reached within 24 hours.[31] This maximum concentration achieved within 24 hours was comparable to the steady-state concentration achieved by Letendre et al following administration of multiple single doses (0.1 mg/kg).[30] These studies suggest use of a single loading dose (0.3 mg/kg) followed by the recommended dosing (0.1 mg/kg) to more quickly achieve and maintain plasma firocoxib concentrations.

In a group of 390 horses with lameness due to chronic, naturally occurring OA, daily administration of firocoxib paste (0.1 mg/kg) resulted in improvement in lameness in 70.7% of horses after the first 7 days of treatment and 78.7% after 14 days of treatment.[32] Improvement in lameness was most rapid within the first 7 days of treatment and continued at a slower rate through day 14. It is important to note that results of this study should be interpreted with caution, knowing that no control population was included in this study. A similar study evaluated the effect of varying doses (0.05 mg/kg, 0.1 mg/kg, and 0.25 mg/kg) of firocoxib paste or a vehicle control on naturally occurring lameness due to OA or navicular syndrome when administered for 7 days.[33] Results found that all doses increased peak vertical force compared with the control group, but the increase occurred more quickly with the higher doses (0.1 mg/kg and 0.25 mg/kg). No significant difference was identified in lameness score or peak vertical force between doses of 0.25 mg/kg and 0.1 mg/kg, providing evidence to suggest 0.1 mg/kg may be an effective dose for reducing naturally occurring, chronic lameness in horses.

A single study has compared the effects of oral firocoxib paste (0.1 mg/kg q24) to oral phenylbutazone (4.4 mg/kg q24) in horses with naturally occurring lameness due to OA. Overall results found firocoxib to be efficacious at controlling pain and improving function in horses with chronic OA and this improvement was observed to a similar degree as with phenylbutazone.[34] When looking at more specific variables, including pain on joint manipulation, joint circumference and range of motion, horses receiving firocoxib had a significantly greater improvement over horses receiving phenylbutazone. Based on these studies, firocoxib may be efficacious in the management of chronic orthopaedic pain in horses and may have a lower risk of side effects; however, this has not been demonstrated in clinical studies.

Other systemically administered NSAIDs that have been used in horses include meloxicam, carprofen, ketoprofen, etodolac and ketorolac. Meloxicam is considered a COX-2-selective NSAID; however, its COX-2 selectivity is diminished with higher doses.[15,35] Meloxicam is approved for use in horses in multiple countries as an oral suspension or injectable and administered at 0.6 mg/kg once daily; however, an equine formulation is not available in the United States. Studies have shown meloxicam to reduce lameness in experimental models of both foot lameness and synovitis.[36-38] Meloxicam administration (0.6 mg/kg q24) for 7 days following lipopolysaccharide-induced synovitis also reduced the amount of carpal joint effusion and carpal circumference when compared with a placebo.[38] A recent study has investigated the effect of meloxicam on movement asymmetry as measured by a commercially available inertial measurement unit. Results found that meloxicam did not change or reduce movement asymmetry identified; however, the movement asymmetry identified was not determined to be the result of lameness.[39] A study comparing phenylbutazone (4.4 mg/kg PO once) and meloxicam (0.6 mg/kg PO once) administration following induction of two different models of experimentally induced lameness found meloxicam to be better at decreasing lameness associated with a lipopolysaccharide synovitis model.[36] Phenylbutazone administration was found to be superior in lameness reduction during a heart bar shoe model of foot pain. Authors postulated the differences seen in this study may be related to differential COX-1 and -2 expression in the different models and the difference in COX selectivity of phenylbutazone versus meloxicam.[36]

Carprofen is licensed for use in small animals in the United States, and formulations are available for the treatment of musculoskeletal disorders and postoperative inflammation in horses in Europe and Canada. Carprofen is a chiral compound and commercial preparations are available as 50:50 mixture of both R- and S-enantiomers. When compared with phenylbutazone and flunixin meglumine, carprofen is a more selective inhibitor of COX-2 and has also been found to inhibit activation of the proinflammatory transcription factor NFK-B.[35,40] Recommended dosing for carprofen is 0.7 mg/kg IV or 1.4 mg/kg PO once daily. McKellar et al found both oral (1.4 mg/kg PO) and intravenous (0.7 mg/kg IV) administration of carprofen to horses and ponies to be well tolerated after 14 days of administration.[41] Few clinical studies have evaluated the efficacy of carprofen for orthopaedic pain and lameness in horses. In a study mentioned above that evaluated postoperative analgesia,[29] horses that received carprofen (0.7 mg/kg IV) had similar postoperative pain scores to those

administered flunixin meglumine (1.1 mg/kg) or phenylbutazone (4 mg/kg).[29] In horses that required additional analgesia following surgery, the time interval after surgery where this was needed was comparable between horses receiving carprofen (11.7 hours) and those receiving flunixin meglumine (12.8 hours). Anecdotal evidence has suggested that carprofen may be a good alternative to phenylbutazone in cases exhibiting renal and gastrointestinal side effects secondary to phenylbutazone administration.[42]

Ketoprofen exists as a chiral molecule composed of R- and S-enantiomers. Studies have found that ketoprofen is not bioavailable when given orally, and therefore should only be administered intravenously or intramuscularly.[43] Recommended dosing for ketoprofen is 2.2 mg/kg once daily. Following intravenous or intramuscular administration, similar mean free S- to free R- serum concentration ratios were found.[44] In horses with chronic hoof pain and laminitis, administration of an equimolar amount of ketoprofen (3.63 mg/kg IV) reduced hoof pain and lameness to a greater degree than when horses received a 4.4 mg/kg dose of phenylbutazone.[45] When horses in this study received the recommended dose of ketoprofen (2.2 mg/kg IV), similar changes in hoof pain indices and subjective lameness scores were observed to horses administered phenylbutazone (4.4 mg/kg phenylbutazone IV). In an experimental model of synovitis, administration of phenylbutazone (4.4 mg/kg IV) resulted in significantly reduced lameness scores while ketoprofen at the recommended (2.2 mg/kg IV) or higher dose (3.63 mg/kg IV) did not reduce lameness scores.[46] No change in synovial fluid total nucleated cell count or the differential cell count was seen between treatment groups. Synovial fluid total protein in the phenylbutazone group was increased at 12, 24 and 48 hours when compared with both ketoprofen groups. All treatment groups resulted in reduction in synovial fluid PGE2; however, this effect was sustained over a longer period of time for the phenylbutazone group. Overall, the authors concluded that based on the results, phenylbutazone may be a more useful treatment for horses with acute synovitis or joint inflammation when compared with ketoprofen.[46] It is important to note that NSAIDs were administered prior to induction of synovitis and therefore may not reflect results seen in clinical cases where disease and subsequent clinical signs are present prior to treatment.

Etodolac also exists as a racemic mixture of R- and S-enantiomers. It is available as an intravenous or oral formulation and is considered a selective COX-2 inhibitor.[47] Doses of 20 mg/kg and 23 mg/kg have been described for use in horses.[47-49] A majority of studies examining effects of etodolac in horses have focussed on its effect on the gastrointestinal tract. In a study of acute LPS-induced middle carpal joint synovitis, lameness was seen in 4/6 horses that did not receive treatment, in 3/6 horses that received etodolac (23 mg/kg IV q12) and in 2/6 horses that received phenylbutazone (4.4 mg/kg IV q12).[47] Another study looking at the effects of etodolac in horses with naturally occurring navicular syndrome found horses receiving 23 mg/kg etodolac had an improvement in lameness as demonstrated by increased mean peak vertical force at 6, 12 and 24 hours after oral administration.[49] This study also found that administration of etodolac every 12 hours had no increased analgesic effect when compared with administration every 24 hours. No adverse effects were seen with etodolac administration in either of these studies.

Few studies have evaluated ketorolac tromethamine, an injectable non-selective COX inhibitor commonly used in human orthopaedics and sports medicine, for use in horses. A pharmacokinetic study found ketorolac to be rapidly absorbed following a single intramuscular or oral dose (0.5 mg/kg) with no adverse effects identified.[50] Another study found ketorolac (0.5 mg/kg) and flunixin meglumine (1.1 mg/kg) to suppress LPS-induced prostaglandin E2 and thromboxane B2 production to a similar degree in vitro for up to 12 hours.[51] This same study also found no adverse effects with ketorolac administration (0.5 mg/kg IV q12) for 3 days. Phenylbutazone (4.4 mg/kg IV q24) was found to be more effective at reducing lameness secondary to the heart bar model of hoof pain when compared with ketorolac (2 mg/kg IV q12) and flunixin meglumine (1.1 mg/kg IV q12).[52] Further studies are needed to evaluate the efficacy of ketorolac for the management of orthopaedic pain in horses.

Diclofenac, a topical NSAID, is available as a 1% diclofenac sodium liposomal cream and is licensed in the United States for the control of pain and inflammation associated with OA of the tarsus, carpus, fetlock and pastern joints in horses. Recommended dosing is the application of a 5-inch ribbon (73 mg) of topical cream up to twice daily over the affected joint for up to 10 days. A study comparing the application of diclofenac to a control in horses with naturally occurring OA found a significant improvement in overall subjective lameness scores following 5 days of treatment with a twice daily application of diclofenac.[53] This group also found that horses receiving diclofenac treatment had improvements in lameness regardless of the chronicity or severity of their disease. In an experimental carpal chip model for OA induction, horses receiving topical diclofenac treatment (7.3 g q12) had a reduction in lameness similar to horses administered phenylbutazone (2 g PO q24); however, there was no difference in flexion score or joint effusion when compared with either treatment group or a control group.[18] Radiographically there was no difference between the diclofenac and phenylbutazone group; however, on MRI the phenylbutazone group had greater degrees of sclerosis compared with the diclofenac or control groups. In an experimental nonsurgical model of acute synovitis, no difference was seen in lameness scores, carpal temperature or carpal circumference in horses receiving a twice daily treatment with topical diclofenac compared with the control.[54] Based on the results of these studies, diclofenac may be not be as effective for acute synovitis cases as it is for more chronic OA cases.

In summary, a single experimental study found firocoxib to be as effective as phenylbutazone in reducing lameness in horses with naturally occurring lameness due to osteoarthritis. Firocoxib at the labelled dose (0.1 mg/kg PO) requires multiple days to reach a steady-state plasma concentration; however, this can be expedited by administration of a single loading dose (0.3 mg/kg PO) followed by the labelled dose. Anecdotally, phenylbutazone is thought to be more effective and preferred by equine practitioners for reducing inflammation and lameness due to orthopaedic disorders. Further studies are needed to elucidate the differences in effectiveness of

phenylbutazone and firocoxib. Other COX-2-selective NSAIDs, such as meloxicam, carprofen, and etodolac, have been found to be effective in reducing lameness in horses. Meloxicam was shown to be superior at decreasing lameness in an experimental model of synovitis when compared with phenylbutazone, indicating it may be useful in cases of acute synovitis. The COX-2-selective NSAIDs can be used to decrease the risk of side effects associated with chronic NSAID administration and may offer an alternative in cases exhibiting side effects secondary to NSAID administration where continued NSAID administration is required.

2 | EFFECTS OF NSAIDS ON MUSCULOSKELETAL TISSUES

Due to the widespread use of NSAIDs for the treatment of orthopaedic pathologies, it is important to understand the effects of these medications on bone, cartilage, synovium and orthopaedic soft tissue structures. Prostanoids and other arachidonic acid metabolites play an important role not only in the normal physiology of these tissues, but also in the response to pathology and injury; therefore, understanding the effects of their blockade on normal metabolism, function and healing of these tissues is essential.

When looking at joints in particular, it is important to remember that homeostasis is a result of the interplay among all components, including the articular cartilage, subchondral bone, joint capsule, synovium and synovial fluid. Therefore, the role NSAIDs play on each of these tissues when treating orthopaedic disease must be considered.

2.1 | Articular cartilage

Multiple studies, both in-vitro and in-vivo, have examined the effects of different NSAIDs on articular cartilage breakdown products, proinflammatory cytokines and cartilage catabolic proteins in normal and abnormal joints.

To determine the effect of carprofen on healthy cartilage, varying concentrations of R-enantiomer, S-enantiomer and racemic carprofen were added to the culture media of equine chondrocytes and cartilage explants. A significant difference in proteoglycan synthesis was seen between the enantiomers, with the S-enantiomer having the greatest stimulatory effect at 12.5 μg/mL. At higher doses than what is achieved with clinical dosing (125 μg/mL), inhibition of proteoglycan synthesis was identified with both enantiomers.[55] When cartilage explants were incubated with proinflammatory cytokine IL-1B, carprofen decreased release of matrix metalloproteinases and concentrations of fibronectin, a cartilage degradation product.[56] Another study looked at the effect of carprofen on LPS-stimulated chondrocytes and found the S-enantiomer of carprofen to attenuate the increase in IL-6 seen with LPS stimulation; however, neither the R- or S-enantiomer of carprofen nor the racemic carprofen changed IL-1 release.[57] Based on these studies, carprofen did not suppress release of proinflammatory cytokine IL-1; however, it may mitigate the catabolic effects of IL-1 on cartilage through decreased matrix metalloproteinase activity. The S-enantiomer of carprofen may provide chondroprotective properties through stimulation of proteoglycan synthesis.

In a carpal chip model of OA, Frisbie et al examined the effect of topical diclofenac (7.3 g applied q12, 14 days) and phenylbutazone (2 g PO q24, 14 days) on gross and histologic features of OA. Total gross cartilage erosion scores were decreased in osteoarthritic joints treated with diclofenac compared with osteoarthritic joints treated with phenylbutazone, although no significant differences in glycosaminoglycan concentrations were identified.[18] Histologically, safranin-O staining was increased in the diclofenac-treated group compared with the phenylbutazone-treated group, indicating higher concentrations of proteoglycan content in the cartilage of horses in the diclofenac-treated group compared with the phenylbutazone-treated group. Authors concluded that diclofenac produced disease-modifying effects, as it appeared to mitigate some effects of OA on the articular cartilage, when compared with controls and phenylbutazone-treated horses. It is important to note that the dose of phenylbutazone used in this study is at the low end of the dosing interval, and this could account for some of the differences seen between the phenylbutazone and diclofenac groups.

De Grauw et al evaluated the effect of meloxicam (0.6 mg/kg PO q24, 7 days) in an LPS-induced synovitis model on concentrations of inflammatory mediators and cartilage extracellular matrix components in synovial fluid.[38] Meloxicam treatment significantly lowered matrix metalloproteinase activity and resulted in significantly lower concentrations of glycosaminoglycans and cartilage cleavage fragments. These effects were most significant following initial induction of the synovitis model and indicate that meloxicam administration may be beneficial against matrix metalloproteinase-mediated cartilage degradation in cases of acute synovitis.

Another study by this same group examined the effect of phenylbutazone (2 mg/kg PO q12, 7 days) in an LPS-induced synovitis model and found no difference in general matrix metalloproteinase activity in synovial fluid from horses treated with phenylbutazone versus horses treated with the placebo.[58] Similarly, Clegg et al did not find any effect of phenylbutazone or flunixin meglumine on matrix metalloproteinase-2 or -9 activity in gelatin or casein degradation assays.[59] DeGrauw et al also found no effect of phenylbutazone treatment on concentrations of glycosaminoglycan or collagen cleavage fragments that increased following induction of acute synovitis. These findings indicate phenylbutazone administered at the dosage used in this study failed to suppress inflammation-induced changes to cartilage in acute synovitis.[58]

Cartilage explants from normal horses administered a 14 day course of phenylbutazone (4.4 mg/kg PO q12) found suppression of proteoglycan synthesis to a similar degree to that of cartilage explants incubated with IL-1B.[60] This is in contrast to findings by Fradette et al where no significant difference was detected in markers of cartilage synthesis and degradation in serum or synovial fluid in horses administered a 10 day course of phenylbutazone (4.4

mg/kg PO q12, 3 days then 2.2 mg/kg q12, 7 days) versus control horses.[61] This is further in contrast to a study where cartilage explants cultured with varying clinically relevant phenylbutazone concentrations had suppression of proteoglycan loss associated with explant culture.[62]

Variation in study design and in the amount and timing of phenylbutazone administration makes comparison of these studies difficult. Results suggest that there might be differing effects of phenylbutazone on normal versus diseased joints and would advocate for judicious use in horses with joint disease or known cartilage damage. Given that phenylbutazone is one of the most common NSAIDs used for orthopaedic disease, further investigation of its effects on musculoskeletal tissues is warranted.

2.2 | Synovium

Multiple studies have been performed to evaluate the effects of NSAIDs on clinical markers of inflammation and on concentrations of inflammatory mediators produced from cultured synoviocytes and in synovial fluid from live horses.

Both R- and S-enantiomers of carprofen and the racemic mixture were found to attenuate release of IL-6 from LPS-stimulated synoviocytes, but had no effect on IL-1 concentrations.[57]

In an amphotericin B-induced model of acute synovitis, topical diclofenac application (5 inch ribbon applied twice daily) did not have any effect on total protein, cell count or IL-1 concentrations compared with the control treatment.[54] Interestingly, this group found the prostaglandin E2 concentrations to be significantly higher in the diclofenac-treated group compared with the control group at 24 hours after induction of synovitis. The authors proposed this unexpected finding to be a result of individual variation, low case numbers and the intense inflammatory nature of the amphotericin B synovitis model. In a carpal chip model of OA, diclofenac application did not significantly affect total protein concentration or glycosaminoglycan concentration in synovial fluid.[18] This study also found similar findings following phenylbutazone administration (2 g PO q24, 14 days). Interestingly, phenylbutazone was found to significantly attenuate the increase in prostaglandin E2 when compared with both the diclofenac and control groups.

Morton et al evaluated the effect of etodolac (23 mg/kg IV q12) and phenylbutazone (4.4 mg/kg IV q12) in a lipopolysaccharide (LPS)-induced model of acute synovitis. Both etodolac and phenylbutazone reduced the LPS-mediated increase in synovial fluid white blood cell count at 6 and 24 hours following induction of the model.[48] Similarly, both treatments significantly reduced prostaglandin E2 concentrations in synovial fluid at 6 hours following LPS injection. Concentrations of thromboxane B2 were significantly reduced in LPS-injected joints of horses treated with phenylbutazone compared with other treatment groups. Due to inhibition of prostaglandin E2 with minimal change in thromboxane B2 concentrations, the authors concluded etodolac may provide more selective anti-inflammatory properties while producing similar clinical responses to phenylbutazone in cases of acute synovitis.

Meloxicam (0.6 mg/kg PO q24, 7 days) was not found to affect synovial fluid white blood cell count, cell differential or protein concentrations following intra-articular LPS injection.[38] Meloxicam-treated horses have lower concentrations of synovial fluid prostaglandin E2 and substance P at 8 hours post injection in addition to decreased synovial fluid bradykinin concentrations at 24 hours post injection. These changes in synovial fluid prostaglandin, substance P, and bradykinin correlated with improved lameness variables at 8 and 24 hours. These findings suggest that meloxicam reduces pain in acute synovitis mediated by prostaglandin E2 in addition to pain as a result of increases in substance P and bradykinin concentrations.

A similar study by the same group did not find an effect of phenylbutazone administration (2 mg/kg PO q12, 7 days) on synovial fluid white blood cell count or substance P concentration following LPS injection.[58] However, the phenylbutazone-treated group did see the synovial fluid total protein return to normal more quickly compared with the control group. These results are in contrast to those of Morton et al, where phenylbutazone administration (4.4 mg/kg IV q12) reduced the LPS-mediated increase in white blood cell count. These studies used differing dosages of phenylbutazone, which may have contributed to these differences.

Moses et al examined the effects of phenylbutazone, flunixin meglumine, ketoprofen, carprofen and meloxicam on synovial explants incubated with and without LPS on prostaglandin E2 and hyaluronan concentrations.[63] In the non-stimulated group, there was no effect of any of the drugs tested. In the stimulated explants, meloxicam was found to reduce prostaglandin E2; however, there was no difference in hyaluronan production among groups.

2.3 | Bone

Few studies have investigated the effects of NSAIDs on bone metabolism or bone healing in horses. One study found no significant differences in biomarkers of bone resorption (CTX-1) or formation (OC) in serum from horses administered a 10 day course of phenylbutazone (4.4 mg/kg PO q12, 3 days then 2.2 mg/kg q12, 7 days) compared with control horses, indicating that phenylbutazone administration did not markedly affect bone turnover.[61]

Rohde et al examined the effect of a 14 day course of phenylbutazone (4.4 mg/kg PO q12) on bone healing following a unicortical tibial bone biopsy in normal horses. No difference was detected among treatment and control horses in osteonal density or osteonal activity.[64] Mineral apposition rate was significantly decreased in the phenylbutazone-treated group when compared with the control group. The percentage of mineralised tissue within the cortical defect increased between day 14 and 30 in the control group; however, this was not observed in the horses treated with phenylbutazone. Conclusions of this study indicate that phenylbutazone was found to decrease some measures of bone activity and administration may affect early phases of bone healing following injury.[64]

2.4 | Tendon/ligament

To the authors' knowledge, no published studies exist to date have investigated the effects of NSAIDs on tendon healing in horses.

A study carried out in rabbits evaluated the effect of flunixin meglumine (2 mg/kg IM, q24) on tendon healing following deep digital flexor tendon transection and repair.[65] Four weeks post transection and repair, the rabbits in the flunixin meglumine group exhibited a higher number of blood vessels, less cellularity and the presence of longitudinally oriented collagen fibres at the site of repair when compared with the control group. The repair sites in the control group had highly cellular granulation tissue and no longitudinally oriented collagen fibres. With mechanical testing, the flunixin meglumine-treated group had significantly higher ultimate and yield loads, energy absorption and ultimate stress compared with the control group. Authors concluded that treatment with flunixin meglumine improved both structural and mechanical properties of repaired tendon in rabbits; however, this is difficult to extrapolate to our equine patients.

The differences observed in these studies highlight the varying effects that individual NSAIDs have on musculoskeletal tissues. Based on responses seen in normal versus abnormal models, it is also likely that NSAIDs have differing effects on diseased tissues. Based on the dearth of information available on commonly used NSAIDs and their effects on musculoskeletal tissues, further studies are warranted.

3 | ASSESSMENT OF THE FUTURE MANAGEMENT OF PAIN AND INFLAMMATION IN EQUINE ORTHOPAEDICS

Due to their efficacy, wide availability and low cost, NSAIDs are and will continue to be a mainstay in the management of orthopaedic injury and lameness in horses despite their potential downsides. Identifying strategies to decrease the systemic side effects associated with NSAID administration has been a recent focus of both human and veterinary medicine. Further development of COX-2-selective NSAIDs, the development of prostaglandin receptor antagonists, the local delivery of NSAIDs and adjunct treatments to ameliorate side effects are innovations that will contribute to the future of NSAID use in the management of pain and inflammation in equine orthopaedic disease.

3.1 | COX-2-selective NSAIDs

The development and investigation of COX-2-selective NSAIDs will likely be important in the future of NSAID use in veterinary medicine. Celecoxib is a commonly used COX-2-selective NSAID in humans for treatment of OA and has a higher safety profile for the gastrointestinal tract.[66] Few studies have evaluated the use of systemic celecoxib in veterinary medicine, and of those performed, a majority have occurred in dogs.[67-69] In an experimental model of OA in dogs, gross and histologic cartilage damage, macroscopic synovial inflammation and proteoglycan turnover were not different between celecoxib-treated and control groups despite lower synovial PGE2 in the celecoxib-treated group.[68] Pharmacokinetic studies of celecoxib have been performed in horses; however, the efficacy of systemic administration of this drug for treatment of orthopaedic disease in horses has not been investigated.[70]

Robenacoxib is a novel COX-2-selective NSAID developed solely for use in veterinary medicine. Robenoxib is different from other COX-2-selective NSAIDs, including firocoxib, in that it lacks a sulphur-containing group.[71] Initial studies in rats found robenacoxib to have minimal gastrointestinal or renal effects, even at high doses.[71] In cats undergoing soft tissue or orthopaedic surgery, those treated with robenacoxib had lower pain scores than cats administered meloxicam.[72] Robenacoxib administration was found to be safe for the treatment of OA in cats as clinical gastrointestinal, liver or kidney damage was not identified compared with controls. A subset of these cats had both OA and chronic kidney disease, and no difference was seen in outcome in cats with or without concurrent chronic kidney disease following robenacoxib administration.[73] In dogs with OA secondary to cranial cruciate disease, robenacoxib improved lameness and radiographic scores.[74] Only one study has been performed evaluating robenacoxib administration in horses.[75] This study identified the COX-2 selectivity of robenacoxib in horses and evaluated its effect on recovery of jejunal mucosa after ischaemia. Results indicated that recovery of barrier function after ischaemia was not affected by robenacoxib administration, as the transepithelial resistance was similar to control horses.[75] No studies have been performed to investigate the pharmacokinetics of robenacoxib in horses or its efficacy in orthopaedic disease. Based on its efficacy in cases of OA in small animals, robenacoxib could prove useful in the treatment of equine orthopaedic disease and lameness.

As COX-2-selective NSAIDs become more popular for treatment of equine orthopaedic disease, clinicians have to be cognisant that these medications are not devoid of side effects; though there is an impression cited that both renal and gastrointestinal side effects are lower compared with the traditional, non-selective NSAIDs, the evidence for this is quite limited.

In horses administered phenylbutazone (4.4 mg/kg PO) or firocoxib (0.1 mg/kg PO) once daily for 10 days, squamous and glandular ulcer scores were higher in horses from both treatment groups compared with control horses at day 10.[76] Squamous ulcer scores were no different between the phenylbutazone and firocoxib groups, but glandular ulcer scores were higher in the phenylbutazone group when compared with the firocoxib group. Faecal microbiota evaluated in a similar study found the microbiota of the control group to remain stable while both phenylbutazone and firocoxib-treated horses experienced decreased diversity and a change in the microbiota profile.[77] The clinical implication of this in horses is unknown.

In humans, constitutive expression of COX-2 has been identified in certain tissues and cell types.[78] In addition to the development

and investigation of COX-2 inhibitor drugs for use in horses, further research into the constitutive COX-2 expression in horses is indicated to fully understand the systemic effects of these medications.

3.2 | Prostaglandin receptor antagonists

Prostanoid receptor antagonist drugs block the action of prostanoids at specific receptors responsible for inflammation and pain, while allowing normal function at receptors important for homeostatic functions. Prostanglandin E2 (PGE2) is an important mediator of inflammation and pain and acts at four different receptors: EP1, EP2, EP3 and EP4.[79] The EP4 receptor is primarily responsible for PGE2-mediated inflammation and sensitisation of sensory neurons.[80] Grapiprant selectively binds to the EP4 receptor and is currently approved by the FDA for the control of pain and inflammation associated with OA in dogs. Due to the selectivity for the EP4 receptor, grapiprant should have fewer adverse effects when compared with the selective and non-selective COX-inhibiting medications. When compared with a control, grapiprant alleviated pain associated with OA in client owned dogs.[81] During the 28-day study period, occasional vomiting was identified in a higher percentage of treated dogs versus the control; however, no other side effects were identified. In a safety study where a 25-fold increase over therapeutic dosing was administered (50 mg/kg PO) to dogs daily over 9 months, only mild gastrointestinal disturbances, such as loose, mucoid or haemorrhagic faeces, were identified.[82] Blood and urinary samples collected from these dogs during the study period remained within the reference intervals. Two studies have been performed evaluating the pharmacokinetics of grapiprant in horses.[83,84] When grapiprant was administered to horses orally at the therapeutic dose for dogs (2 mg/kg), the drug was well tolerated; however, the effective concentration required for pain control in dogs was not achieved in horses.[83] Based on these studies, there is no clinical evidence currently that grapiprant could be an alternate to NSAID administration in horses.

3.3 | Anti-nerve growth factor monoclonal antibodies

Nerve growth factor (NGF) is a tumour tissue-produced soluble growth factor released by tissues in response to the production of inflammatory mediators.[85] Interaction of NGF with its receptor, tropomyosin receptor kinase A, leads to signalling important in pain initiation and maintenance, and NGF levels are elevated in a variety of chronic pain conditions.[85] Anti-nerve growth factor monoclonal antibodies serve to sequester NGF and prevent interaction of it with its receptor and downstream pain signalling. Anti-nerve growth factor monoclonal antibodies administered intravenously have been shown to reduce pain in human, canine and feline patients with OA.[86-88] Intravenous administration of equinised anti-nerve growth factor monoclonal antibodies did significantly affect pain or imaging parameters of horses with experimentally induced OA.[89] Intra-articular administration of these antibodies in an IL-1-induced model of acute synovitis did produce improvements in pain and disease modifying effects in the synovial membrane and fluid parameters.[89] Further studies are warranted; however, anti-nerve growth factor monoclonal antibodies may be an alternative to NSAID treatment in horses with chronic orthopaedic disorders.

3.4 | Local delivery of NSAIDs

Another future strategy for the use of NSAIDs in equine orthopaedic disease includes local, targeted delivery of these medications through direct intra-articular injection, sustained release materials and topical application. Local administration produces higher, therapeutic concentrations of these medications at the site of inflammation compared with concentrations achievable following systemic administration. Additional benefits of local administration include the requirement of a lower dose, the ability to use drugs with a low bioavailability, decreased systemic side effects and longer intervals between treatments. In human medicine, intra-articular administration of ketorolac for treatment of OA and postoperative pain has shown promising results.[90-93] Studies evaluating the intra-articular administration of ketorolac compared with intra-articular triamcinolone acetonide in human patients with knee OA found similar efficacy and significant improvement in pain scores in both groups.[91,92] Studies evaluating the safety of intra-articular NSAIDs in human and animal models have found mixed results and further research is needed to investigate the effects on cartilage and soft tissue structures.[90,93]

In horses, few studies have been performed evaluating the intra-articular use of NSAIDs or sustained drug release products. Intra-articular injection of a high dose of celecoxib (1.25 mg/kg) in polyethylene glycol was performed in four horses and celecoxib was detected in synovial tissue after 10 days, indicating sustained joint exposure.[94] No clinical signs of joint inflammation or lameness were identified in these horses; however, gross and histologic evidence of granulomatous synovitis was seen. The authors proposed this granulomatous reaction to be a result of the high dose of celecoxib used in these horses. A similar study compared the effects of an intra-articular hydrogel to a commercial hyaluronic acid gel in normal middle carpal joints of healthy horses. In this same study, intra-articular administration of a low (50 mg/g) and high dose (260 mg/g) celecoxib-loaded hydrogel was evaluated in the tarsocrural joints.[95] Clinically, no lameness was identified in horses injected with the hyaluronic acid gel, the hydrogel or the low dose celecoxib hydrogel. At 24 hours post injection, horses injected with the high dose celecoxib hydrogel exhibited mild lameness which resolved within 72 hours. Changes were seen in synovial fluid white blood cell count, synovial total protein and GAG content within 24 hours after injection in the hyaluronic acid gel, the hydrogel and the high dose celecoxib hydrogel groups; however, these changes resolved within 72 hours, indicating a transient inflammatory response after the injection of these substances. Histological examination did not

find any major abnormalities or evidence of granulomatous synovitis reported by Larsen et al Synovial fluid concentrations of celecoxib reached a maximum concentration in most horses in both the low and high dose celecoxib hydrogel groups within 8 hours post injection. Synovial fluid concentrations of celecoxib rapidly decreased over 7 days in the low dose group and decreased more slowly in the high dose group with low concentrations of celecoxib detected at 28 days. Authors of this study concluded that this celecoxib-loaded hydrogel could be a successful drug delivery system in the treatment of OA. A similar study performed with low (40 mg/g) and high dose (120 mg/g) celecoxib-loaded hydrogels in an LPS-induced model of synovitis found that both low and high dose celecoxib hydrogels had mild, transient effects on inflammatory and structural synovial fluid biomarkers.[96] The celecoxib concentrations were lower than what was used in the previously mentioned study; however, the low dose and high dose gels showed a similar pattern in synovial fluid celecoxib concentrations, with a more rapid decrease over 7 days in the low dose gel. Further research on the clinical efficacy and long-term safety of celecoxib loaded hydrogels is needed prior to its clinical use in horses.

3.5 | Adjunct therapies

NSAID therapy will continue to be common in the management of equine orthopaedic disorders and clinicians must be aware of new and evolving therapies for preventing and treating the associated side effects. Two recent studies have evaluated adjunct therapies for combating common gastrointestinal side effects associated with NSAID administration. Omeprazole is effective at preventing and treating equine glandular ulcer syndrome and is commonly administered in conjunction with NSAIDs to prevent NSAID-induced gastric ulcers.[97] In a group of horses with evidence of mild equine glandular and squamous gastric disease, horses administered phenylbutazone had increased equine glandular gastric disease compared with horses administered phenylbutazone and omeprazole.[98] Intestinal complications were identified in both phenylbutazone and phenylbutazone/omeprazole-treated groups; however, a significantly greater number of horses in the phenylbutazone/omeprazole group exhibited intestinal complications compared with the control group. Authors concluded that while omeprazole did ameliorate equine glandular gastric disease, it may increase the incidence of intestinal complications. Given the results of this study, continuing to evaluate other adjunct therapies for decreasing the risk of NSAID-related gastrointestinal side effects is important. Another study evaluated the use of a commercially available nutritional therapeutic [Platinum Performance GI, Platinum Performance] important in targeting equine microbiota, and its effects on NSAID-induced gastric and intestinal injury and faecal microbiota.[99] Phenylbutazone administration (4.4 mg/kg PO q24 for 9 days) increased the presence of 16s DNA in whole blood, used as a measure of intestinal permeability, and induced gastric ulceration in the glandular mucosa and changes in the faecal microbiota. Administration of the nutritional therapeutic prevented the increase in 16s DNA, significantly decreased phenylbutazone-induced gastric ulceration and stabilised the faecal microbiota. Further research is needed; however, administration of this nutritional therapeutic may improve phenylbutazone-induced gastrointestinal side effects.

Paracetamol (acetaminophen) is a widely available and commonly used analgesic and anti-pyretic medication.[100] The mechanism of action remains unclear; however, it has been shown to be effective in equine studies with few reported side effects.[101-103] When administered to horses 1 hour following lameness induction with the heart bar shoe model of hoof pain, paracetamol (20 mg/kg, PO) was found to be just as effective in reducing lameness as flunixin meglumine (1.1 mg/kg).[102] A case report described the administration of paracetamol (20 mg/kg PO q12) in conjunction with phenylbutazone (4.4 mg/kg PO q12) for improving comfort in a pony with acute laminitis.[101] Another study evaluated the use of paracetamol as a constant rate infusion (CRI) alone and in conjunction with tramadol on effects of nociception in six healthy adult horses.[103] The group administered paracetamol (6 g/h CRI) in conjunction with tramadol (1 mg/kg bolus followed by 3 mg/kg/h CRI) had reduction in nociception 20 minutes after the infusions were started. There were no differences in nociception in groups administered paracetamol or tramadol infusions alone. Results of these studies indicate that paracetamol administration to horses may be useful in providing multi-modal analgesia to horses with orthopaedic pain while limiting side effects; however, further studies are indicated.

3.6 | Pro-resolving mediators and receptors

As research continues to improve our understanding of inflammation, we are learning more that the complete, non-specific blockade of cyclooxygenase activity and prostaglandin production has negative effects on the healing process of musculoskeletal tissues, particularly tendons and ligaments. In addition to the detrimental effects of prostaglandins during inflammation, beneficial roles have been identified such as promoting immunomodulatory properties and restoring tissue homoeostasis after injury.[104] Recently discovered pro-resolving mediators, such as lipoxins and resolvins, and their receptors, which are stimulated by prostaglandins, are important in controlling inflammation, orchestrating its resolution and returning injured tissue back to its normal state.[105] Because NSAIDs can have detrimental effects on healing of tendon and ligaments, the use of these pro-resolving mediators and receptors are likely to become important in the treatment and management of musculoskeletal disease and injury.[104]

4 | CONCLUSIONS

Orthopaedic disease and OA will continue to be the important problems encountered by equine veterinarians. Control of the inflammatory cascade through the use of systemic and topical

NSAIDs will remain as a mainstay of treatment in these cases. Common non-selective NSAIDs, phenylbutazone and flunixin meglumine, are equally effective in reducing lameness in cases of orthopaedic injury. COX-2-selective NSAIDs, such as firocoxib, are also effective in reducing lameness and in addition decrease, but do not eliminate, the risk of systemic side effects. Studies evaluating the effects of NSAIDs on musculoskeletal tissues highlight many differences in the response of normal and diseased tissue to varying NSAIDs and the need for further research in this area. Multiple innovative strategies, such as more selective inflammatory inhibitors and local delivery of NSAIDs, will shape the future of NSAID use in equine orthopaedics.

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Not applicable.

INFORMED CONSENT

Not applicable.

CONFLICT OF INTERESTS

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