Nonsteroidal Anti-inflammatory Drug Use in Horses

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KEYWORDS

• Nonsteroidal anti-inflammatory drugs • Horses • Analgesia • Anti-inflammatory

KEY POINTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of soft tissue, musculoskeletal, and abdominal inflammation and pain.
- Potential adverse effects associated with NSAIDs include gastrointestinal and renal toxicity and inhibition of bone healing.
- Over the past several decades, the focus has been on developing NSAIDs with more selectivity for cyclooxygenase-2 as a means of decreasing adverse effects while maintaining efficacy.
- As NSAIDs are commonly used in race and performance horses, it is imperative that clinicians are familiar with regulatory recommendations for the use of these drugs before performance.

THE INFLAMMATORY CASCADE

Inflammation is the body's response to tissue damage. In the acute stage, the body attempts to return normal function to the injured and inflamed tissue. However, over time, and with the development of chronic inflammation, deleterious effects can occur. The first step in the inflammatory cascade is the release of arachidonic acid, mediated by Phospholipase A2, in response to insult or injury to cellular membranes. This initiates what is termed the arachidonic acid cascade (**Fig. 1**).

Arachidonic acid serves as a substrate for the generation of a number of eicosanoids, including prostaglandins, leukotrienes, and thromboxane A_2 (TXA_2), all of which play a key role in the inflammatory cascade. Production of prostaglandins and TXA_2 is mediated by Prostaglandin H_2 synthase, otherwise known as cyclooxygenase (COX). Oxygenation of arachidonic acid by COX enzymes forms the unstable prostaglandin G_2, which is subsequently converted to prostaglandin H_2. Conversion to specific

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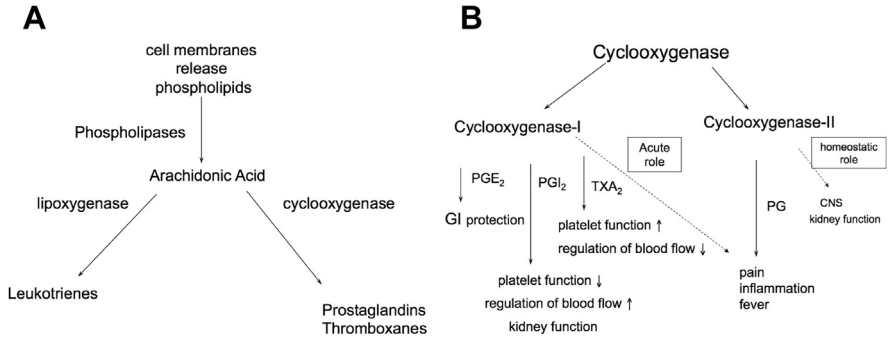

Fig. 1. Arachidonic acid cascade (*A*) and role of cyclooxygenase enzymes (*B*).

prostaglandins (ie, prostaglandin E_2 [PGE_2], prostaglandin $F_2\alpha$, and TXA_2) depends on the presence of specific isomerase, reductase, or synthase enzymes.[1] These inflammatory mediators are responsible for the sequelae of inflammation, including increased vascular permeability, heat, and decreased nociceptor thresholds.

CYCLOOXYGENASE ENZYMES AND NONSTEROIDAL ANTI-INFLAMMATORY DRUG INHIBITION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes. To date, 3 COX enzymes have been identified, COX-1, COX-2, and COX-3. COX-1 and COX-2 have been well characterized (see **Fig. 1**), but less is known about COX-3. COX-1 is constitutive and present in nearly all cell types.[2] It has been deemed the "housekeeping" enzyme, as it plays a role in normal physiologic functions that help to maintain homeostasis. This includes such things as gastroprotection, gestation, and parturition. COX-2 on the other hand is constitutively expressed in most cell types with protein levels increasing in a matter of hours following stimulation.[3,4] COX-2 can be upregulated as much as 20-fold in endothelial and other cell types as part of the inflammatory process.[5–8] COX-2 induction occurs following exposure to stimuli associated with inflammation including bacterial lipopolysaccharide (LPS) and inflammatory cytokines, such as interleukins 1 and 2 and tumor necrosis factor alpha.[9] Conversely, expression of COX-2 is decreased in the presence of anti-inflammatory cytokines such as interleukins 4, 10, and 13.[3,10,11] Although in most tissues COX-2 is considered pathologic, this an oversimplification as this enzyme does contribute to homeostasis in some organs. COX-2 is constitutively expressed in certain regions of the brain[12,13] and plays a role in maintaining blood flow in the compromised kidney.[14] However, because COX-1 appears to have a greater importance in maintaining homeostasis than does COX-2, most adverse effects of NSAID administration are associated with inhibition of this enzyme (see discussion later in this article).

CYCLOOXYGENASE-1/CYCLOOXYGENASE-2 SELECTIVITY

Over the past 2 decades, the focus, both in human and veterinary medicine, has been on developing NSAIDs that are more selective for the COX-2 enzyme as compared with COX-1.[15] Depending on the relative degree of selectivity, this would ideally preserve the normal housekeeping functions of COX-1 while inhibiting the proinflammatory and potentially detrimental effects often associated with COX-2. However, as discussed previously, although minimal, the contribution of COX-2 to normal physiologic functions should be considered when selecting a COX-2 selective NSAID.

The degree to which NSAIDs inhibit the different COX isoforms and therefore their relative selectivity, is determined by in vitro COX inhibitory assays. Selectivity for the isoforms is expressed as an inhibitory ratio, usually the IC_{50} for COX-1: IC_{50} for COX-2, in which IC_{50} is the plasma concentration necessary to inhibit 50% of COX activity.[16] The higher the ratio, the more selective the NSAID is for COX-2.[16] The inhibitory ratio allows for classification of NSAIDs with specificity for COX-2 as "COX-2 preferential" or "selective," and those with no significant effect on COX-1 as "COX-1 sparing." More recently, some investigators have described selectivity using an IC_{80} or IC_{95} ratio, suggesting that this may be more clinically applicable as often times a high level of prostaglandin inhibition is necessary to achieve a therapeutically useful antipyretic, anti-inflammatory, or analgesic effect.[17,18]

It is important to note that NSAID COX-1:COX-2 selectivity varies between species[19] and therefore extrapolation of classification as a COX-2 selective or preferential inhibitor between species should be done with caution. Even within the same species, variability in inhibitory ratios between studies may be observed. Variability in the assay used, including incubation time, exogenous or endogenous substrate (arachidonic acid), use of whole cells or microsomes and presence or absence of plasma proteins in the media, can yield very different inhibitory ratios.[16] To encourage consistency, whole blood assays have been deemed the gold standard for determining COX inhibition.[16] Most inhibitory ratios reported in the literature for horses have used this assay system. Because inhibition is measured in blood samples obtained from the species of interest, the whole blood assay is considered the most physiologically relevant assay. In this assay, NSAID inhibition (IC_{50}, IC_{80}, or IC_{95}) of COX isoforms is assessed by measuring prostaglandin E_2 (PGE_2) concentrations in LPS-stimulated macrophages as a measure of COX-2 inhibition and TXB_2 concentrations in platelets as a measure of COX-1 inhibition, following incubation of different concentrations of the NSAID of interest.[20] The presence of plasma proteins in whole blood is another advantage to the whole blood assay. Most NSAIDs are highly plasma protein bound and therefore the presence of plasma proteins makes the assay more representative of the in vivo environment.[21] The whole blood assay can also be used to measure ex vivo inhibition in samples collected from animals following administration of NSAIDs in vivo. This allows for determination of COX inhibition under clinical conditions and at therapeutically achievable drug concentrations.[16]

NONSTEROIDAL ANTI-INFLAMMATORY DRUG CYCLOOXYGENASE INHIBITION IN HORSES

Inhibitory ratios (IC_{50} COX-1: IC_{50} COX-2) for selected NSAIDs used in equine medicine are listed in **Table 1**. Phenylbutazone (PBZ), flunixin meglumine (FLU), and ketoprofen (KTP) are all considered COX-1 selective NSAIDs,[18,19,22] whereas meloxicam, an NSAID approved for use only in dogs in the United States, is more selective for COX-2 than COX-1 in the horse.[22] The classification of carprofen is a little more ambiguous, with one group of investigators classifying it as nonselective[18,19] and another group as COX-2 selective.[22]

COXIBS AND CYCLOOXYGENASE INHIBITION

The coxibs are a subset of NSAIDs that were first introduced in human medicine several years ago with the promise of the same anti-inflammatory effects as other NSAIDs but with a reduction in toxicity. Coxibs are COX-2 selective and COX-1 sparing at the same time. This group of drugs is structurally different from traditional

Table 1
Inhibitory ratios (IC_{50} COX-1: IC_{50} COX-2) for nonsteroidal anti-inflammatory drugs in horses

Drug	Reference	IC_{50} COX-1: IC_{50} COX-2
Phenylbutazone	Brideau et al,[19] 2001	1.6
	Beretta et al,[22] 2005	0.30
Flunixin meglumine	Brideau et al,[19] 2001	0.3
	Beretta et al,[22] 2005	0.34
Ketoprofen	Landoni & Lees,[54] 1996	0.48
Firocoxib	Kvaternick et al,[24] 2007	268–643
Carprofen	Brideau et al,[19] 2001	1.6
	Beretta et al,[22] 2005	2.0
	Lees et al,[18] 2004	3.3
Meloxicam	Beretta et al,[22] 2005	3.8
Deracoxib	Davis et al,[29] 2010	25.7

NSAIDs in that they have a tricyclic ring and a sulfone or sulfonamide group.[23] The resultant bulky structure limits their ability to bind to the COX-1 site, thus decreasing inhibition of this enzyme. The COX-2 binding site is much larger, so coxibs are able to bind and thus "selectively" inhibit COX-2 activity.

Currently there are 4 coxibs approved for use in animals: deracoxib, firocoxib, mavacoxib, and robenacoxib. It should be noted that mavacoxib is not currently approved for use in the United States and only firocoxib is labeled for use in horses. The COX-1 sparing and COX-2 inhibitory effects of firocoxib have been demonstrated in a number of ex vivo studies.[24–27] Kvaternick and colleagues[24] reported a COX-1/COX-2 inhibitory ratio ranging from 268 to 643 (see **Table 1**). COX-2 was significantly inhibited following a single intravenous (IV) administration with PGE_2 levels decreased by 83.0% $\pm$ 22.9%.[26] Following a single oral administration, PGE_2 levels were decreased by 53.0% $\pm$ 41.1% relative to baseline.[26] Inhibition was greater following once-a-day administration for 7 days with PGE_2 levels decreased by 79% $\pm$ 8%.[25] The greater inhibition following multiple dose administration suggests a lag time until the maximal therapeutic effect is achieved and is likely attributable to the long elimination half-life for firocoxib (>24 hours).[24,26,28] A loading dose may be prudent to shorten the time to reach a therapeutic response.

Although not approved by the Food and Drug Administration (FDA) for use in horses, deracoxib (a coxib approved for use in dogs) has a COX-1/COX-2 IC_{50} ratio of 25.7 and a COX-1/COX-2 IC_{80} ratio of 22.1.[29] So, although not as COX-1 sparing/COX-2 selective as firocoxib, deracoxib appears to be much more COX-2 selective then traditional NSAIDs (PBZ, FLU, and KTP) in the horse.

THERAPEUTIC USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

In horses, NSAIDs are used primarily for the treatment of soft tissue, musculoskeletal, and abdominal inflammation and pain. There are currently 6 NSAIDs approved by the FDA that are labeled for use in the horse. These include FLU, PBZ, KTP, diclofenac (DLC), meclofenamic acid, and firocoxib (**Table 2**). Other NSAIDs have been investigated in the horse and are discussed here; however, it is important to note that administration of drugs in a species other than one in which they are approved by the FDA constitutes extralabel drug use (ELDU) and therefore ELDU regulations as described in the Animal Medicinal Drug Use and Clarification Act (AMDUCA) apply.

Table 2
Nonsteroidal anti-inflammatory drugs approved by the Food and Drug Administration for use in horses

Drug	Formulation	Route	Dose, mg/kg
Phenylbutazone	Tablets, paste, powder	PO	4.4 mg/kg q24h 2.2 mg/kg q12h
	Injectable	IV	4.4 mg/kg q24h 2.2 mg/kg q12h
Flunixin meglumine	Injectable Paste, granules	IV, IM PO	1.1 mg/kg q24h 1.1 mg/kg q24h
Ketoprofen	Injectable	IV	2.2 mg/kg q24h
Firocoxib	Injectable Tablets, paste	IV PO	0.09 mg/kg q24h 0.1 mg/kg q24h
Diclofenac	Liposome cream	Topical	73 mg (5 inch strip) q12h
Meclofenamic Acid	Granules	PO	2.2 mg/kg q24h

Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth; q, every.

Musculoskeletal Pain and Inflammation

NSAIDs remain the mainstay of treatment for horses with musculoskeletal pain and inflammation, with PBZ remaining the most commonly prescribed NSAID. PBZ is an effective anti-inflammatory both in experimental models as well as naturally occurring chronic forelimb lameness.[30,31] The effects of both PBZ (4.4 mg/kg IV once per day for 4 days) and FLU (1.1 mg/kg IV once per day for 4 days) have been studied in navicular syndrome.[32] Significant improvement in force plate and clinical lameness evaluations were noted following administration of both NSAIDs compared with the saline control group.

The COX-2 selective NSAID, firocoxib, is effective in the treatment of naturally occurring osteoarthritis with improved lameness scores and mobility observed following chronic administration.[33] Improvement was most rapid within the first 7 days of treatment with continued improvement occurring at a slower rate for the next 7 days.[33] The effectiveness of firocoxib in treating osteoarthritis is comparable to that reported for PBZ.[34] In a randomized controlled clinical trial, Doucet and colleagues[34] demonstrated comparable improvement in a number of lameness parameters (lameness score, joint swelling, joint circumference, and range of motion) for PBZ paste (4.4 mg/kg by mouth every 24 hours) and firocoxib paste (0.1 mg/kg by mouth every 24 hours).

Although not approved for use in horses in the United States, meloxicam is commonly used in equine practice in other countries. Its efficacy in horses has been established for the management of orthopedic postoperative pain and inflammation.[35] Experimentally, meloxicam (0.6 mg/kg by mouth every 24 hours for 7 days) is effective in the treatment of acute synovitis,[36] producing a significant reduction in lameness and effusion and decreased synovial fluid biomarkers of inflammation, matrix metalloproteinase activity, and cartilage turnover.[36]

DLC is an NSAID used extensively in human medicine. Currently the only DLC product approved for use in veterinary medicine is a topical liposomal preparation, labeled for the control of pain and inflammation associated with osteoarthritis in horses. The purported benefit to this formulation is the lack of systemic absorption. It is applied and acts locally, and as such the potential for adverse side effects reported for systemic administration of NSAIDs is minimized. The efficacy of this preparation in the treatment of inflammatory conditions in the horse has yielded highly variable results

and may be somewhat dependent on the inflammatory model used. In one study, Caldwell and colleagues[37] reported that a single topical administration of DLC resulted in DLC concentrations in transudate that significantly attenuated carrageenan-induced local production of PGE_2.[37] In a second study, DLC was used for the treatment of inflammation in a model of acute synovitis in horses.[38] The investigators of this study found no overall difference between the treatment and control groups in this model of inflammation. Also somewhat confounding was the increase in synovial PGE_2 concentrations in the DLC-treated horses as compared with the control group. This is in stark contrast to the study by Caldwell and colleagues,[37] in which PGE_2 concentrations decreased after DLC administration. Most recently, Frisbie and colleagues[39] reported on the use of DLC to treat horses with experimentally induced osteoarthritis. The results of this study led the investigators to conclude that there was a significant improvement in clinical lameness in horses treated with the DLC cream.

Colic

NSAIDs are routinely used to reduce the effects of endotoxemia and visceral pain in patients with colic and colitis.[40,41] In the case of gastrointestinal injury, endotoxin may be released, which stimulates phospholipase A2 and subsequent eicosanoid production as a result of induction of COX-2 enzymes. The most commonly used NSAID for the treatment of colic and associated endotoxemia is FLU. Experimentally, FLU has been shown to be effective in reducing the acute systemic side effects and preventing clinical signs of endotoxemia, including cardiovascular and hemodynamic alterations, hypoxemia, and lactic acidosis.[42,43] Although not used as commonly under clinical conditions, experimentally PBZ also has been shown to be effective in preventing adverse effects associated with endotoxemia.

Although FLU remains one of the mainstays for the treatment of colic, inhibition of repair mechanisms in the injured intestine and a reduction in intestinal motility following administration of nonspecific COX inhibitors has been well established.[44–46] In response to mucosal injury, intestinal villi contract, epithelial cells surrounding the denuded basement membrane migrate into the defect, and tight junctions between the apical epithelial cells are assembled to close the paracellular spaces and repair barrier integrity. Contraction of the intestinal villi and assembly of tight junctions are under the control of prostaglandins and are dependent on increases in COX enzymes. Inhibition of COX enzymes, as occurs with NSAID administration, can therefore interfere with healing of the gastrointestinal tract following injury. Although nonselective NSAIDs such as FLU slow mucosal recovery in ischemic-injured jejunum, the COX-2 selective NSAID firocoxib does not appear to affect recovery.[46] As the degree of visceral analgesia was comparable between the NSAIDs, the investigators suggested that firocoxib may be advantageous in horses recovering from ischemic intestinal injury.

Analgesia

It is well established that PGE_2 lowers nociceptor thresholds and can therefore potentiate the effects of substances that cause pain.[47–49] During inflammatory pain, prostaglandins (primarily PGE_2) are generated at peripheral terminals of sensory neurons causing hyperalgesia.[50,51] In addition to acting at peripheral sites, there is evidence that NSAIDs also act centrally to reduce hyperalgesia.[52] In addition to inhibition of PGE_2 production in the central nervous system, other central mechanisms mediated by endogenous opioid peptides as well as inhibition of serotonin or excitatory amino acids have been proposed.[53]

NONSTEROIDAL ANTI-INFLAMMATORY DRUG PHARMACOKINETICS

The pharmacokinetics of NSAIDs have been extensively reported and therefore the reader is referred to the literature for a more detailed discussion of the pharmacokinetics of these compounds. Select pharmacokinetic parameters are listed in **Table 3**. In general, NSAIDs are lipid-soluble, weak organic acids that are well absorbed following oral administration. Absorption of PBZ appears to be high regardless of the formulation. Conversely, oral absorption of KTP appears to be dependent on the specific formulation.[54,55] The bioavailability of KTP was less than 5% for an oil-based formulation, 50% when administered in a gelatin capsule[54] and 69% and 88.2% for the S (+) and R (−) enantiomers, respectively, when the FDA-approved injectable formulation (water soluble) was administered orally.[55] Food can have profound effects on the absorption of NSAIDs.[26,56] For PBZ and FLU, administration with food delays the rate of absorption but generally does not affect the extent of absorption. In vitro studies showed greater than 98% and 70% binding of drug to feed for PBZ and FLU, respectively. When administered with food, the extent of firocoxib absorption is decreased (decreased area under the curve).[26]

Most NSAIDs have relatively small volumes of distribution (0.1–0.3 L/kg) attributable to a high degree of plasma protein binding (PPB; 95%–99%). Firocoxib is an exception with a volume of distribution of 1.7 L/kg.[24,26] Although PPB limits distribution across membranes for most NSAIDs, it does allow for accumulation of NSAIDs in inflammatory exudate. Inflammatory exudate is high in plasma proteins and the high degree of affinity of NSAIDs for these proteins leads to sequestration of drug at sites of inflammation. Studies using tissue cage models have demonstrated comparable and in some cases higher concentrations of NSAIDs in inflammatory exudate in horses administered FLU, KTP, PBZ, and carprofen.[57] PPB in inflammatory exudate may also explain the prolonged duration of action of NSAIDs in spite of the short elimination half-life and only once or twice a day dosing.

The high degree of PPB limits glomerular filtration and therefore limits excretion of most NSAIDs as parent compound. Instead most NSAIDs undergo extensive hepatic metabolism to inactive metabolites. Phenylbutazone is an exception in that biotransformation produces the active metabolites, oxyphenbutazone and gamma-hydroxyphenylbutazone, which contribute to the anti-inflammatory and analgesic properties of the compound. With the exception of firocoxib, most NSAIDs have a relatively short elimination half-life. The elimination half-life for firocoxib is more than 24 hours in horses,[24,26,55] and with a once-a-day dosing interval, significant bioaccumulation occurs with concentrations at steady state being 3 to 4 times higher than after a single dose.[24,55] With a prolonged elimination half-life, time to steady state can be prolonged for firocoxib, and therefore a loading dose may be prudent to achieve maximal therapeutic effect more rapidly.

ADVERSE EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Gastrointestinal

The effects of NSAIDs on intestinal healing following an ischemic injury were discussed previously. Another commonly reported gastrointestinal adverse effect associated with NSAID use is gastric ulceration. This usually occurs following overdose (high dose administration), chronic administration, or in susceptible populations (ie, foals). These effects are attributed to both local irritation as well as decreases in cytoprotective prostaglandins. COX-1 and COX-2 are constitutively expressed in the gastrointestinal tract. COX-1 plays a major role in gastroprotection in both the healthy and diseased animal. It mediates the production of prostaglandins, such as PGE_2,

Table 3
Select pharmacokinetic parameters for commonly used nonsteroidal anti-inflammatory drugs in horses

Drug	Test Dose	Vd, L/kg	CL, mL/min/kg	$T_{1/2}$, h
Phenylbutazone				
Lees et al,[75] 1987	4.4 mg/kg IV	0.141	0.298	5.46
Flunixin meglumine				
Knych et al,[76] 2015	1.1 mg/kg IV	0.137 ± 0.012	0.767 ± 0.098	4.83 ± 1.59
Lee & Maxwell,[77] 2014	1.1 mg/kg IV	0.157 ± 0.022	1.04 ± 0.27	3.38 ± 1.14
Ketoprofen				
Knych et al,[55] 2016	2.2 mg/kg IV	0.344 ± 0.044 (R(−)) 0.298 ± 0.025 (S(+))	5.75 ± 0.55 (R(−)) 2.78 ± 0.27 (S(+))	2.49 ± 0.077 (R(−)) 2.86 ± 0.102 (S(+))
Landoni & Lees,[54] 1996	2.2 mg/kg IV	0.128 (R(−)) 0.117 (S(+))	5.77 (R(−)) 6.62 (S(+))	1.98 (R(−)) 1.09 (S(+))
Firocoxib				
Holland et al,[26] 2015	57 mg	1.81 ± 0.59	0.71 ± 0.188	31.1 ± 10.6
Knych et al,[28] 2014	1.9 mg/kg IV q 24 h 5 d	3.66 ± 1.44[a]	0.725 ± 0.180[a]	39.4 ± 17.7[a]
Kvaternick et al,[24] 2007	0.1 mg/kg IV	1.70 ± 0.53	0.611 ± 0.221	29.6 ± 7.5

Abbreviations: CL, total systemic clearance; IV, intravenous; q, every; $T_{1/2}$, terminal elimination half-life; Vd, volume of distribution.
[a] Parameters were calculated after the last dose.

which are responsible for decreasing hydrochloric acid secretion and increasing mucosal bicarbonate and mucus production, effects that protect the stomach from the erosive effects of gastric acid. Ulceration following NSAID administration is usually a result of interference with mucosal protective mechanisms. Because the gastroprotective mechanisms are associated primarily with COX-1, administration of COX-2–selective NSAIDs have been proposed as an alternative to avoid gastric ulcer formation. An alternative mechanism to gastric ulcer formation by the NSAIDs was proposed by Martinez and colleagues.[58] These investigators suggested that ulcer formation may be due to oxidative stress that resulted from PBZ overdose (4.4 mg/kg once per day by mouth for 5 days, followed by a single 13.2 mg/kg IV dose on day 6).[58]

Right dorsal colitis is another reported adverse effect associated with NSAIDs, especially PBZ administration.[59] Diarrhea, often mild (ie, cow pie consistency), and signs of colic often in conjunction with hypoalbuminemia are commonly observed. Similar to gastric ulcers, right dorsal colitis is thought to be a result of inhibition of protective prostaglandins that simulate mucous production and maintain blood flow to the colon.[60]

Renal Toxicity

PGE_2 and PGI_2 play key roles in the regulation of renal blood flow, water excretion, and electrolyte balance. Production of both are under the control of COX-1 and COX-2, both of which are constitutively expressed in the kidneys. In the hydrated animal, COX inhibition by NSAIDs likely has little effect on renal hemodynamics; however, when an animal is dehydrated, loss of prostaglandin production can result in vasoconstriction of the afferent arteriole, loss of medullary perfusion, and redistribution of blood flow to the renal cortex. The likelihood of renal toxicity does not appear to be decreased because COX-2 plays a key role in renal homeostasis.

Bone and Wound Healing

Although studies are limited in veterinary species, there is substantial evidence from human and rodent studies that NSAIDs inhibit bone healing. The exact mechanism of action is unknown, but the predominant theory is that NSAIDs inhibit prostaglandin synthesis, therefore interfering with cell signaling and leading to an uncoordinated healing process.[61] Effects on bone healing appear to be most pronounced in the early phases of bone healing[62–65] and are reversible on discontinuation of treatment.[63,66–71] Inhibition of bone healing is equally as likely with COX-2 selective as with COX-1 selective NSAIDs[62,63,66–73] because there is evidence that inflammation stimulated by the COX-2 enzyme is essential for fracture healing.

USE IN PERFORMANCE HORSES

NSAIDs are commonly used as part of treatment regimens for sports-related injuries in horses and because of their ability to affect performance, their use is tightly regulated

Table 4
Recommended thresholds and withdrawal times for nonsteroidal anti-inflammatory drugs under the model rules for horseracing

Drug	Route	Dose, mg/kg	Plasma Threshold	Withdrawal, h
Flunixin meglumine	IV	1.1	20 ng/mL	32
Ketoprofen	IV	2.2	2.0 ng/mL	24
Phenylbutazone	IV	4.0	2.0 μg/mL	24

Abbreviation: IV, intravenous.

Table 5
Recommended thresholds and withdrawal times for nonsteroidal anti-inflammatory drugs for performance horse events

Drug	Route	Dose, mg/kg	Threshold, μg/mL	Withdrawal, h
Firocoxib	Oral	0.1	0.240	>12
Flunixin meglumine	Oral, IV	1.1	1.0	>12
Ketoprofen	IV	2.2	0.250	>12
Meclofenamic acid	Oral	2.2	2.5	>12
Naproxen	Oral	10	40.0	>12
Phenylbutazone	Oral, IV	2.2	15.0	>12

in these horses. Specific NSAIDs that are allowed, the permitted threshold concentration, and withdrawal time recommendation may vary from discipline to discipline and between regulatory groups (**Tables 4** and **5**). Although regulations for horse racing can vary between racing jurisdictions, many individual states have adopted the Racing Commissioners International's "Model Rules" (see **Table 4**). Equestrian disciplines, other than horse racing, usually follow the recommendations of the US Equestrian Federation or the Federation Equestrian International. Alternatively, individual breeds or disciplines may develop their own recommendations. Recommendations change occasionally, so it is important to visit the organization's Web sites periodically for updates (**Box 1**).

Regardless of the governing body, the intent is to establish regulatory thresholds at a concentration in which the drug has no or minimal pharmacologic activity and can be effectively regulated. In the United States, to establish appropriate regulatory recommendations, a pharmacokinetic study is conducted and a statistical approach is then used to establish a withdrawal time that is representative of the time that drug concentration will fall below the threshold value, plus a statistical margin of safety.[74] The recommended withdrawal time is based on a specific drug formulation, route of administration and dosage, and therefore if treatment deviates in any way it may be necessary to extend the withdrawal time recommendation accordingly. A published withdrawal time recommendation in the United States does not constitute a guarantee, warranty, or assurance that the use of the therapeutic medication at the dosage listed will not result in a positive post-race test. The treating veterinarian must still do his or her own risk assessment based on relevant clinical factors.

Box 1
Web sites for various equestrian disciplines

Horseracing	http://ua-rtip.org/industry_service/arci_model_rules
Model Rules Racing Medication and Testing Consortium (RMTC)	http://rmtcnet.com
US Equestrian Federation (USEF)	http://www.usef.org
Federation Equestrian International (FEI)	http://www.fei.org
American Quarter Horse Association	https://aqha.com
National Cutting Horse Association	http://www.nchacutting.com
Tennessee Walking Horse National Celebration	http://twhnc.com

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