NSAIDs: USES AND ADVERSE EFFECTS IN THE HORSE

Jennifer L. Davis, DVM, PhD, DACVIM (LA), DACVCP
College of Veterinary Medicine
North Carolina State University, Raleigh, NC, USA

**FLUNIXIN MEGLUMINE**
Flunixin meglumine (Banamine) is frequently used in horses for the treatment of colic and endotoxemia. It has not historically been used for treating lameness, due to a perceived inferiority to phenylbutazone for musculoskeletal pain. Comparative studies in horses with naturally occurring navicular disease have shown no significant differences in the analgesic effects of flunixin and phenylbutazone, however. Similarly, both flunixin and phenylbutazone have been shown to block endotoxin induced prostanoid production and inflammation. The real benefit of flunixin in treating endotoxemia or colic may therefore lie in the availability of and ease of injection of flunixin.

Flunixin is absorbed well orally. Pharmacokinetic studies of powder and paste formulations show a rapid absorption with peak plasma concentrations occurring at approximately 30 minutes, and an oral bioavailability of 86%. Many people use flunixin intramuscularly, particularly owners. This practice should be discouraged, as flunixin is highly irritating and there are reports of abscessation and clostridial myositis secondary to IM administration. As an alternative to IM injections in the horse, a recent study examined the oral bioavailability of the injectable formulation. Bioavailability of this preparation was approximately 72%, with similar pharmacokinetics to the commercially available oral preparations. This may provide a safer alternative to IM injection for horse owners.

There are 2 commonly used doses of flunixin. The anti-inflammatory and analgesic dose is reported to be 1.1 mg/kg PO or IV q12h. This dose has been shown to produce a maximum effect in animal models. Lower doses (0.25 mg/kg IV q8h) have been studied, however and been shown to be effective in preventing the prostanoid production associated with endotoxin challenge, with presumably fewer side effects, and without masking the signs of colic. The flunixin was given pre-challenge in those instances, and therefore, the efficacy of this dose in clinic cases is often challenged. In fact, using this dose in experimental horses that are repeatedly challenged with endotoxin causes a decrease in thromboxane production, but an increase in certain other prostanoids.

Caution should be used when administering flunixin to newborn foals, due to differences in pharmacokinetics, and an increased risk for gastric and duodenal ulceration. Area under the curve, clearance, and half-life of flunixin are significantly greater in newborn foals compared to adult horses. The half-life increases from 1-2 hours in adults to 6-8 hours in foals. Based on this, dosing intervals should be longer in foals to prevent toxicity of flunixin.

**PHENYLButAZONE**
Phenylbutazone is another popular NSAID used in horses. It is cheap and very effective for treatment of musculoskeletal conditions, including navicular, laminitis, and other causes of lameness. It has also been shown to be effective in preventing prostanoid production after endotoxin challenge; however it is not as effective as flunixin in preventing the cardiovascular changes associated with endotoxin. Phenylbutazone also has a beneficial effect on gut motility and gastric emptying in an endotoxin challenge model.
Oral bioavailability approaches 91%. Injectable products of phenylbutazone have good oral bioavailability as well. The time to peak plasma concentration is greatly affected by feeding, particularly with a hay diet. Inadvertent peri-vascular administration of many injectable phenylbutazone products can cause severe tissue necrosis and sloughing. If the injection is made in the left side of the neck, the vagosympathetic trunk, the left recurrent laryngeal nerve, and the esophagus may all be damaged. Phenylbutazone has two major metabolites, oxyphenbutazone and γ-hydroxyphenbutazone, which account for approximately 25-30% of the administered dose. The pharmacokinetics of phenylbutazone are dose-dependent, with higher elimination half-lives reported after higher dosing. Phenylbutazone pharmacokinetics are altered in newborn foals and therefore should be used with caution.

Phenylbutazone has a higher incidence of adverse events in the horse when compared to flunixin and ketoprofen. In instances of gastric ulceration, this may be related to a direct cytotoxic effect after oral administration. The toxic effects are greatly amplified in horses that are anorexic or dehydrated.

**Ketoprofen**

Ketoprofen is not absorbed orally or rectally, therefore parenteral administration is necessary. It is less irritating than flunixin or phenylbutazone, therefore repeated intramuscular injections rarely cause problems. Ketoprofen is available as a racemic mixture of the R(-) and S(+) enantiomers. It is the S(+) enantiomer that is responsible for the anti-inflammatory activity, whereas the R(-) enantiomer provides the analgesic effects of the drug. Only the S(+) enantiomer is associated with the toxic effects of the drug. Unfortunately, due to chiral inversion, the S(+) enantiomer predominates in the horse. Nevertheless, ketoprofen has a higher therapeutic index than either flunixin or phenylbutazone, with fewer adverse effects noted when used at the label dose. Ketoprofen is not as effective in reducing lameness scores in animals with navicular disease. Clinical efficacy in endotoxemia and other inflammatory syndromes is similar, however higher doses may be required to get a comparable effect. Initially, it was though that ketoprofen had the ability to block both the COX and lipooxygenase (LOX) pathways in arachidonic acid metabolism. It does not appear to do this at clinically relevant plasma concentrations, however.

**Firocoxib**

Firocoxib is a non-steroidal anti-inflammatory drug introduced in the United States in 2005. It is labeled for use in the horse as a paste preparation for oral administration at a dose of 0.1 mg/kg for 14 days for the treatment of osteoarthritis. In 2011, it was also approved as an injectible formulation for IV administration at 0.09 mg/kg for 5 days. Firocoxib is a highly COX-2 selective, with COX 1:COX-2 IC₅₀ ratios of 263-643. Efficacy testing has shown a similar response to phenylbutazone in naturally occurring lameness.

In safety studies, oral ulcers were detected at 3x and 5x the label dose, however no other adverse effects were noted. However adverse effects may still occur, particularly in patients with pre-existing disease, or those that receive NSAID stacking. A recent study examining the effects of co-administration of firocoxib with phenylbutazone showed significantly higher serum creatinine, significantly lower total protein, and a significantly lower urine specific gravity following 10 days of treatment at commonly used doses.

Pharmacokinetics in adult horses show good oral absorption with a long half-life and significant accumulation when the drug is administered once daily. Based on these factors, it may take multiple days for steady concentrations and maximum efficacy to be reached. To overcome
this, a loading dose of 0.3 mg/kg once has been recommended. The administration of the single loading dose allowed achievement of average steady state drug concentrations faster, and after the LD, firocoxib at 0.1 mg/kg every 24 h was able to maintain a relatively constant average drug concentration which should produce less variability in onset of action and efficacy.

In foals, the pharmacokinetics differ from adult horses. Firocoxib is more rapidly absorbed, with a higher maximum concentration, but a shorter half-life, resulting in less drug accumulation. Steady is achieved after approximately 3 doses. In healthy foals, no clinically apparent adverse effects were noted after 9 days of oral firocoxib at 0.1 mg/kg. Intravenous data in foals suggests the difference in pharmacokinetics is due to an increased clearance.

Another area of recent research with firocoxib is into the bioequivalence of the equine and canine formulations. Data suggests the canine formulation is absorbed in the horse and may also be used as an effective anti-inflammatory agent. Multiple dose regimens produce similar plasma half-lives and comparable COX-2 inhibition. The use of the canine formulation is controversial, however. The canine formulation is often administered due to the decreased cost, but the AVMA has stated that they will not support the practice and has issued the following statement: “Since there is a firocoxib product, Equioxx®, labeled for use in horses, then the canine product cannot be used in an extra-label fashion. Selecting the canine product over the equine product for any reason, including economic, is not acceptable. It is only if or when the approved equine drug were judged clinically ineffective for that labeled use that a veterinarian could use another animal approved drug, in an extra-label manner.”

**Diclofenac**

Diclofenac is a non-specific COX inhibitor that may also help inhibit the LOX pathway by reducing arachidonic acid release from cells, as well as enhancing its reincorporation into triglycerides. There are no reports of the use of diclofenac as a systemic anti-inflammatory agent in equine medicine, however topical preparations are available. A 1% liposomal cream is available in the US for topical treatment of joint inflammation. It has good effects on pain and lameness scores, with minimal systemic absorption, and therefore minimal adverse effects. A topical ophthalmic preparation is also available.

**Meloxicam and Piroxicam**

Meloxicam is a COX-2 selective inhibitor labeled for use as an anti-inflammatory drug in the horse. It is typically given as an injection, however oral bioavailability is nearly complete, and absorption is not affected by feeding. PK-PD analysis has shown a maximum effect at approximately 0.2 µg/mL, which translates into a daily dose of 0.6 mg/kg. This dose has proven effective in lameness models, as well as experimental models of colic and abdominal pain.

Another NSAID in this group, piroxicam, has recently received some attention in equine medicine, not for treatment of lameness or colic, but for the treatment of squamous cell carcinomas. Some tumors, particularly SCC, have been shown to produce COX-2. Treatment with piroxicam has produced long-term remissions of SCC in the bladder, urethra and periocular structures. Adverse effects, even at the low doses used (0.2 mg/kg PO q24h) have been noted, and include diarrhea and abdominal pain. It is not known at this time whether or not meloxicam would have a similar effect, with a higher safety profile.
**Etodolac**

Etodolac is a relatively selective COX-2 inhibitor in the horse. It has been used clinically in horses with a previous history of gastric or colonic ulceration, as well as in a few horses with active GI disease, with apparent benefits. The optimum dose to use is still questionable at this time, however. Originally, 20 mg/kg PO q12h was used. More recently, 20 mg/kg PO q24h was shown to be just as effective in treatment of navicular disease. It is possible even lower doses may be used. This would be beneficial, as *in vitro* testing shows that etodolac is a very potent COX-inhibitor in the horse, and although it is selective at lower concentrations, this selectivity may be lost at the doses that have been previously reported.

**Carprofen**

Carprofen is generally considered to be a COX-2 selective or COX-1 sparing drug, with a higher safety profile than other commonly available NSAIDs. The exact mechanism of action of carprofen still receives some debate, however, due to its weak effects on COX-2 specific PGE₂ production *in vitro*. In horses, its peripheral effects on prostanoid production are much less than either flunixin or phenylbutazone, but its analgesic effects are similar. Like ketoprofen, carprofen is available as a racemate, and it is thought that the R(-) enantiomer may have some centrally-mediated analgesic effects.

**Deracoxib**

Following PO administration to horses, deracoxib had a long elimination half-life with an average maximum plasma concentration of 0.54 μg/mL at 6.33 ± 3.44h. Results of *in vitro* COX selectivity assays showed that deracoxib was selective for COX-2 with a COX-1/COX-2 ratio of 25.67 and 22.06 for the IC(50) and IC(80), respectively. Dosing simulations show that concentrations above the IC(80) for COX-2 would be maintained following 2mg/kg PO q12h, and above the IC(50) following 2mg/kg PO q24h. Deracoxib may offer a useful alternative for anti-inflammatory treatment of various conditions in the horse.

**Adverse Effects of NSAIDs**

**Gastric Ulceration**

NSAID administration is frequently associated with gastric ulceration and this has been well documented to occur under experimental conditions. The majority of ulcerations documented following NSAID administration are in the glandular mucosa, although minor ulcerations in the squamous mucosa have been seen. The pathophysiology is typically thought to be due to a decreased production of prostaglandin E₂ (PGE₂) which is responsible for maintaining mucosal blood flow in the stomach and the intestines. It is also responsible for mucosal healing in cases of pre-existing disease. In the stomach, inhibition of cyclooxygenase can also increase acid secretion, decrease output of mucus and bicarbonate, impair vasodilation, and diminish epithelial restitution, cell division, and angiogenesis. Diagnosis is easily made by gastroscopic examination of the squamous and glandular mucosa. Sucralfate is the major mucosal protectant used for treatment of ulcers in horses. H₂ antagonists include such drugs as ranitidine, cimetidine, and famotidine. Of these, ranitidine is most commonly used in horses, due to a more consistent oral absorption and a demonstrated effect on increasing gastric pH. Omeprazole is a proton pump inhibitor and is considered the most effective drug in horses. Pharmacologic treatment of gastric ulcer disease in the horse is likely to be temporary unless environmental and dietary changes are also instituted. Increasing turnout, allowing the horse to graze for extended periods during the day, feeding high
calcium diets, such as alfalfa hay, and decreasing stress during training will all help contribute to ulcer healing and prevention.

**Right Dorsal Colitis**

Right dorsal colitis (RDC) is associated with mucosal ulceration, edema, neutrophilic inflammation and mural thickening of the right dorsal colon. The etiology is thought to be similar to gastric ulceration. It is not known why this particular segment of the intestine is affected greater than other areas. This condition has been diagnosed in horses given toxic doses of NSAIDs, in particular phenylbutazone, however it has also occurred in horses receiving recommended doses. It appears to be precipitated by dehydration and anorexia, therefore NSAIDs should be used with caution in horses that are not eating or drinking well. Horses will show varying signs of colic and diarrhea, and often have a low plasma protein concentration. Dehydration and clinical signs of endotoxemia may be present. Ultrasonography of the 11-13\textsuperscript{th} intercostal space shows a thickened (>1cm) right dorsal colon. One of the mainstays of treatment includes dietary management directed toward providing a low-bulk diet in the form of a pelleted concentrate and restricting or eliminating ingestion of roughage is recommended. Misoprostol, a synthetic analog of prostaglandin E\textsubscript{1}, can be administered orally starting at doses of 5 μg/kg every 12 hours or 2 μg/kg every 6 hours. Some horses will develop signs of abdominal discomfort or diarrhea at these dosages, so lower doses may be necessary. Feeding psyllium mucilloid may promote colonic healing in horses with RDC. Crystalloids as well as colloidal fluids can be administered for treatment of hypovolemia and hypoproteinemia. Plasma may also be beneficial as a colloid, as well as for treating signs of endotoxemia. Prognosis in cases of RDC is usually guarded, due to the risk of colonic rupture or stricture.

**Renal Papillary Necrosis**

Inhibition of PGE\textsubscript{2} and PGI\textsubscript{2}, both of which are involved in the regulation of renal blood flow and cause vasodilation of renal blood vessels, may result in a toxic injury to the kidney. These effects are greatly exacerbated in dehydrated patients, due to an already compromised renal blood flow. The lesions are characterized by medullary crest or papillary necrosis, which is thought to be because the medulla normally receives less blood flow than the cortex, making it more vulnerable to insult. The most consistent laboratory finding is decreased urine specific gravity. This results from preferential damage to areas of the kidney that contribute most to concentrating urine (medulla, papilla). Some horses with NSAID toxicosis will be azotemic. In acute NSAID toxicosis, there may be overt hematuria, or the urinalysis may reveal occult blood, and increased white blood cells. In chronic cases, other than decreased urine specific gravity, urinalysis results are typically normal. Cessation of NSAID administration, fluid therapy, diuretics and correction of electrolyte imbalances are the hallmarks of treatment. The prognosis is significantly related to the duration of renal compromise prior to diagnosis, as well as response to fluid therapy. Horses that remain oliguric or anuric after aggressive therapy have a guarded prognosis.

**Co-administration of NSAIDs**

Some practitioners use the practice of stacking NSAIDs by administering 2 drugs with the same mechanism of action concurrently, in order to increase their efficacy. Some combinations, particularly phenylbutazone and ketoprofen, appear to be synergistic when given together. This is probably due to the quicker onset of action of ketoprofen, and the longer duration of action of phenylbutazone. The downside to this practice is the increased risk of toxicity that occurs when
NSAIDs are administered concurrently. One study showed that horses administered a combination of phenylbutazone and flunixin at the recommended doses for 5 days had a higher incidence of gastric ulceration, as well as a significant decrease in blood proteins concentrations when compared to placebo treated horses, as well as horses receiving phenylbutazone alone. It is likely that the benefits of giving 2 NSAIDs at once are far outweighed by the risks.