FIROCOXIB

Firocoxib is a nonsteroidal antinflammatory 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 injectable formulation for IV administration at 0.09 mg/kg for 5 days. Firocoxib is a highly COX-2 selective, with COX-1:COX-2 IC\textsubscript{50} 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 3 x and 5 x the label dose; however, no other adverse effects were noted. However, adverse effects may still occur, particularly in patients with preexisting disease, or those that receive NSAID stacking. A recent study examining the effects of coadministration 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 suggest the canine formulation is absorbed in the horse and may also be used as an effective antinflammatory 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\textsuperscript{®}, 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."
Opiates
Butorphanol is an opiate drug with \(\kappa\) receptor agonist and \(\mu\) receptor antagonist effects. For post-operative colics, it is administered as a CRI at 13 \(\mu\)g/kg/hr for 24 hours after surgery. This dosage rate has been shown to significantly improve behavior scores, significantly reduce plasma cortisol levels, and lower the weight lost after surgery, compared to controls. The time to passage of first feces was also delayed in these horses, but this was not considered clinically significant. If a CRI is not practical, similar effects can be achieved by adding 10-20 mg of butorphanol to a 5 L bag of LRS and administering at a rate of 1-2 L/hr. The rate can be adjusted if the horse begins to show adverse effects.

Fentanyl is a very potent \(\mu\) receptor agonist that also decreases the release of neurotransmitters involved in pain perception (ie Substance P). Transdermal administration does not produce consistent plasma concentrations for analgesia in all horses and absorption is highly dependent on anatomical placement. Intravenous administration did not produce analgesia in a colic model, except at concentrations that produced opiate-like side effects (CNS excitement).

Tramadol is a \(\mu\) receptor agonist, but it also has effects on norepinephrine and serotonin reuptake. It is considered a mild analgesic, but it can be used in combination with NSAIDs. At this time, clinical experience is lacking with this drug, however experimental studies have shown that a dose of 10 mg/kg PO q12h is safe and produces plasma concentrations expected to be therapeutic.

Buprenorphine is a partial \(\mu\) opioid agonist and can be used for moderate pain, with fewer respiratory side effects than the pure \(\mu\) opioid agonists. However, because it is a partial agonist, there can be a ceiling effect which limits its use in severe pain. The pharmacokinetics of buprenorphine in horses have been studied via the IV, IM and sublingual routes. Both IV and IM injections can cause CNS excitement for a period of time after administration. This effect can be overcome by co-administration with acepromazine or an \(\alpha\)-2 agonist. The sublingual route (0.6 mg/kg) results in low bioavailability, however a pharmacodynamic effects has been noted with this route of administration, with no signs of concurrent CNS excitement.

Anticholinergics
Buscopan (N-butylscopolammonium bromide) has recently been approved by the FDA as a spasmolytic drug for the treatment of abdominal pain in horses caused by spasmodic colic, flatulent colic and simple impactions. It works via an anticholinergic effect resulting from competitive inhibition of muscarinic receptors on intestinal smooth muscle cells. It has been shown to improve pain scores and attitude in treated horses. It has also been shown to facilitate rectal examinations in horses by decreasing rectal pressure and reducing straining during examination. It is only labeled for use as a single injection. Formulations in the UK have been used successfully for years, but these are combined with a NSAID (metamizole). Buscopan should not be used in cases with small intestinal distention, or in cases of colitis. Buscopan will cause an elevated heart rate for up to 30 minutes after injection, eliminating the use of heart rate as an indicator of increasing colic pain.

Alpha-2 Agonists
Romifidine is the newest \(\alpha\)-2 agonist to be approved by the FDA as a sedative and analgesic in horses at a dose of 0.04-0.12 mg/kg IV. It can also be used in anesthetic regimens at 0.1 mg/kg IV, combined with ketamine. It cannot be mixed with acepromazine prior to administration, as precipitation will occur. Romifidine at 0.08 mg/kg is considered to be equipotent to xylazine (1
mg/kg) and detomidine (0.04 mg/kg). Its duration of action is more similar to detomidine, but its sedative effects are less potent. As with other α-2 agonists, romifidine produces a marked decrease in gastrointestinal motility and is associated with the presence of reduced (nonpropulsive) contractions. The cardiovascular effects of romifidine are also similar to other α-2 agonists and include decreased cardiac index, decreased venous oxygenation, increased systemic vascular resistance and arterial blood pressure, and increased incidence of second-degree A-V block.

In some instances, the sedation with α-2 agonists may be too severe or may be causing excessive cardiovascular compromise. In these cases, the drugs can be reversed using several reversal agents. The affinity of atipamezole for alpha-2 receptors is 100 times higher than that of other antagonists. Doses recommended in horses range from 80-200 µg/kg. Atipamezole at a dose of 0.08 mg/kg has been shown to reverse the sedative effects of 0.01 mg/kg of medetomidine in horses. It has also been reported to reverse a severe detomidine overdose in a pony. Doses may need to be titrated to effect. Yohimbine has also historically been used as a reversal agent in horses when administered at doses of 0.075 to 0.15 mg/kg IV.

**DISSOCIATIVE ANESTHETICS**

Ketamine (KET) possesses analgesic and anti-inflammatory activity at sub-anesthetic doses, suggesting a benefit of long-term KET treatment in horses suffering from pain, inflammatory tissue injury and/or endotoxemia. It is a noncompetitive antagonist at N-methyl-D-aspartate receptors in the spinal cord. It also has effects on opioid, monoaminergic, and muscarinic receptors, as well as voltage-sensitive Ca²⁺ channels. It can be used in nerve blocks, as well as epidurally. Constant rate infusions of ketamine have also been studied, however reports of efficacy as an analgesic or anti-inflammatory are conflicting. Doses of 0.8 mg/kg/hr IV were shown to be safe, but not effective based on the pain model described. A more recent study suggested a CRI of 1.5 mg/kg/hr, with higher doses producing an increase in heart rate and respiratory rate. Following a loading dose, administration of 1.5 mg/kg/hr was not associated with any significant effect on the clinical or immunologic response to LPS administration. Ketamine CRI (0.55 mg/kg IV over 15 minutes followed by 1.2 mg/kg/h) delayed gastrointestinal transit time in healthy horses without effect on vital parameters. In horses with chronic laminitis, ketamine (0.6 mg/kg/h) significantly enhanced the analgesic effects of tramadol when administered IV over a 6 hour period. Combined, these studies suggest it may be useful in a multimodal therapy approach, but is not effective on its own.

**ANTICONVULSANTS**

Gabapentin is used in human and small animal medicine for the treatment of neuropathic pain. Recent work has shown that gabapentin binds to the α2δ subunits of voltage dependent calcium channel complexes. These α2δ subunits have been found in numerous tissues in humans and rats, including the brain, and affinity for this binding site has been correlated to the anti-hyperalgesic potency of gabapentin versus other similar drugs. Once bound to the subunit, gabapentin acts in an inhibitory manner, resulting in a decrease in calcium influx in presynaptic nerve terminals and inhibition of the release of excitatory amino acids. We have successfully used gabapentin for the treatment of post-operative neuropathy in a horse at a dose of 2.5 mg/kg PO q8-12h. Other horses may need higher doses. Pharmacokinetic studies show that absorption is low, but due to the long half-life of gabapentin, accumulation occurs. Therefore with multiple doses, therapeutic concentrations can be achieved. We have safely administered up to 10 mg/kg
PO q12h for multiple weeks in some horses without any evidence of deleterious effects. In those horses that are treated for extended periods, we recommend gradually weaning them off the drug, as other species have been known to demonstrate a rebound pain syndrome and/or return of seizure activity.

**Bisphosphonates**

The bisphosphonates are a group of drugs that decrease osteoclastic activity, thereby decreasing bone destruction. As such, they can be used to reduce the risk of fracture and reduce discomfort in cases of skeletal neoplasia. In vitro studies suggest that bisphosphonates also have a direct toxic effect on bone cancer cells and they may inhibit the growth of new blood vessels within the cancer, thereby inhibiting cancer growth. They have a very long duration of action and bind to areas of bone with the highest turnover, only releasing as the bone matrix is remodeled. These drugs are considered to have a wide safety margin, however side effects can include hypocalcemia, gastrointestinal irritation and renal toxicity. Oral administration is associated with severe esophageal ulceration in humans.

Tiludronate has been studied in the horse and proven effective in the treatment of bone spavin, navicular disease, and osteoarticular lesions of the thoracolumbar vertebral column. Tiludronate was also found to significantly reduce bone resorption during immobilization, and prevent long-term osteopenia in immobilized limbs. Two dosing regimens have been studied: 0.1 mg/kg slow IV bolus once a day for 10 days, or 1 mg/kg IV as a single constant rate infusion. Both regimens produce similar plasma exposure and pharmacological effects in horses. The main adverse reactions related to treatment with tiludronate are signs of colic, muscle tremors and sweating. These side effects were observed in less than 5% of horses treated with the recommended therapeutic scheme and could be related to a mild hypocalcemia. Phlebitis, excitaton, hypertonia of the tail and salivation are other possible side effects. Fatigue, recumbency, and, in rare occasions, anaphylactic like reactions such as shock have been reported. To overcome these adverse effects, practitioners have started to use the drug in regional limb perfusions, thereby allowing a smaller total dose to be used and yet still potentially result in high concentrations at the affected sites. Currently, there is no scientific data to support this use. Tildren has recently become licensed in the US for treatment of navicular disease.

Another bisphosphonate has also gained FDA approval and is being marketed in the US. OsPhos® (clodrunate) is also labelled for the treatment of navicular syndrome, but can be dosed IM, with fewer systemic adverse effects. Although clinical experience with this drug is currently lacking, it shows high promise for use in treating lameness caused by bone pain in horses, and may be easier to administer and safer for use in some horses.