Corticosteroids are among the most potent anti-inflammatory medications available. Unfortunately, they carry a high risk of adverse effects, including laminitis, adrenal suppression, Cushing’s-like syndrome and immunosuppression. Injectable steroids are considered the treatment of choice for many allergic/immune-mediated diseases, such as RAO, inflammatory bowel diseases, or skin diseases, however this route of administration does carry the highest risk of adverse effects. Many different routes of administration of glucocorticoids have been tried to help minimize the systemic effects, while providing good anti-inflammatory activity. Other routes, including oral, inhalation, topical, intra-ocular and intra-articular, may be used successfully.

In some cases, pre-existing conditions may limit the use of corticosteroids, therefore alternatives are desirable. For pain and/or inflammation, NSAIDs, or opioids may be used. For RAO/IAD, NSAIDs, antihistamines, PDEI and leukotriene-receptor antagonists have failed to demonstrate therapeutic benefit in horses with heaves. Systemic or inhaled β2 agonists may help, as will environmental changes. For immunosuppression in cases of IMHA, IMTP, pemphigus, or lymphoma, azathioprine (3 mg/kg PO q24h for 30 days, then q48h for 30 days), aurothiomalate (1 mg/kg IM, q7d for 8 weeks), and cyclophosphamide (2.2 mg/kg IV q2-4wk) have all been used, with varying degrees of success. For allergic reactions and dermatitis, antihistamines may be used in mild disease, before signs appear (ie with seasonal disease), or for maintenance once remission has been achieved with steroids. Antihistamines studied in horses include:

- Cetirizine: 0.2-0.4 mg/kg PO q12h
- Hydroxyzine: 0.5-1 mg/kg PO q8h
- Chlorpheniramine: 0.25-0.5 mg/kg PO q6-12h
- Diphenhydramine: 0.67 mg/kg IV
- Pyrilamine: 0.66 mg/kg PO q12h
- Tripelennamine: 1.1 mg/kg IM q6-12h

Antimicrobials as Anti-inflammatories

Tetracyclines have well-known anti-inflammatory properties. They have a demonstrated ability to prevent neutrophil chemotaxis and apoptosis in vitro, although the clinical relevance is questionable at drug concentrations achieved in vivo following oral administration. Doxycycline is reported to decrease the production of pro-inflammatory cytokines, such as matrix metalloproteinases (MMP-8 and MMP-9), interleukin-1 (IL-1), IL-6, and TNF-α, from inflammatory cells. It has also been shown to inhibit staphylococcal exotoxin-induced cytokines and chemokines, and improve the prognosis in a mouse model of endotoxemia. Doxycycline apparently does this by concentrating inside the cell and interfering with intracellular processes. Oral doxycycline may stabilize corneal melting in cases of Pseudomonas keratitis via its anticollagenolytic activity. In cultured human corneal epithelial cells, doxycycline was as effective as methylprednisolone for inhibition of lipopolysaccharide-induced IL-1β and upregulation of the anti-inflammatory IL-1 receptor antagonist. It has also been shown to play a role in ocular surface repair by irreversibly inhibiting
corneal MMP-2 activity. Based on these findings, treatment with systemic doxycycline may be beneficial in horses with corneal ulceration.

Metronidazole and ciprofloxacin have been shown to reduce the clinical severity and gastrointestinal inflammation in humans with Crohn’s disease. Metronidazole has been recommended for the treatment of right dorsal colitis and other nonspecific causes of diarrhea in horses. Both metronidazole and ciprofloxacin have been shown to decrease leukocyte migration through the intestinal cell wall and inhibit intestinal Th1 cytokine production, thereby decreasing inflammation.

The macrolide antibiotics have also been shown to have numerous in vitro, ex vivo and in vivo anti-inflammatory properties and are commonly used in human medicine for adjunct therapy of respiratory disease. Macrolides inhibit neutrophil influx and chemotaxis. Long term use leads to decreased levels of IL-8 (a potent chemoattractant). Levels of IL-6 and intercellular adhesion molecule (ICAM)-1 are also reduced. Tissue damage caused by activated neutrophils and respiratory burst may be decreased due to impaired production of superoxide dismutase. The mechanism behind these actions may be related to an inhibitory effect on NF-κB activation.

**ALTERNATIVE ANALGESIC THERAPIES**

**Opiates**

Butorphanol is an opiate drug with κ receptor agonist and μ receptor antagonist effects. For post-operative colics, it is administered as a CRI at 13 μg/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 μ 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 μ 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 μ opioid agonist and can be used for moderate pain, with fewer respiratory side effects than the pure μ 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 α-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 α-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.

Medetomidine is a highly potent α-2 agonist that has also been studied in horses. At doses of 0.004-0.01 mg/kg, it has similar sedative, analgesic and cardiovascular effects to other, more commonly used drugs. Medetomidine CRIs have been studied as pre-anesthetic and intra-operative regimen with beneficial effects. Dexmedetomidine (3.5 µg/kg IV) produces only short-lived cardiovascular effects, but the short half-life makes it undesirable for bolus dosing, therefore CRIs have also been studied.

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 Ca^{2+} 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 q12h.

**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 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.

Clodronate, Osphos®, is a bisphosphonate recently approved by the FDA. It is similar to tiludronate, Tildren®, both of which are labeled for the control of clinical signs associated with navicular syndrome in the horse. One benefit of clodronate over tiludronate is that it is labeled for intramuscular use at a dose of 1.8 mg/kg (maximum dose of 900 mg/horse), split into 3 separate injection sites. Clodronate may also be associated with fewer adverse effects overall than tiludronate. The main adverse effect with both of these drugs is colic-like symptoms, which have
been reported in 9% of horses receiving clodronate, compared to 41% of horses receiving tiludronate. More clinical experience with clodronate is warranted.