**SMALL ANIMAL PAIN MANAGEMENT**

**Katrina R. Viviano, PhD, DVM**

**CLINICAL PHARMACOLOGY**

**NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)**

NSAIDs act through the inhibition of COX-1 and/or COX-2 enzymes, resulting in anti-inflammatory, anti-pyretic, analgesic, and anti-platelet effects. Cyclooxygenase-1 (COX-1) is constitutively expressed in many tissues (gastrointestinal tract and kidneys) generating protective “housekeeping” prostaglandins. In addition, COX-1 leads to thromboxane production and platelet aggregation. Cyclooxygenase-2 (COX-2) is induced by inflammation-generating pro-inflammatory prostaglandins as well as protective prostaglandins in kidneys. NSAIDs undergo hepatic metabolism and renal elimination. Species differences in metabolism, especially in cats, result in lower dosing or less frequent dosing intervals. The most common side effects include gastrointestinal ulceration, ischemic kidney damage, hemorrhage, and idiosyncratic liver toxicity. The gastrointestinal side effects are due to direct gastric irritation and gastric ulceration. NSAIDs inhibit prostaglandins (PGE2) and alter the hydrophobic kidney damage, hemorrhage, and idiosyncratic liver toxicity. The gastrointestinal side effects are due to direct gastric irritation and gastric ulceration. NSAIDs inhibit prostaglandins (PGE2) and alter the hydrophobic phospholipids in the gastric mucus layer, increasing the risk of gastric ulceration and bleeding. All NSAIDs have the potential to cause GI bleeding, although COX-2 selective drugs may have a lower risk. Ulceration is potentiated by glucocorticoids. In humans, drugs that have been used to prevent NSAID-induced GI ulcers include omeprazole and misoprostol. COX-1 and COX-2 are constitutively expressed in the kidneys and produce renoprotective prostaglandins that increase renal arterial blood flow in response to decreased renal perfusion. COX inhibitors block production of renal protective prostaglandins, increasing the risk of ischemic damage to the kidneys, especially in patients with low renal blood flow. Secondary to COX-1 mediated thromboxane A2 inhibition, platelet function is impaired, resulting in clinical hemorrhage. In dogs, an idiosyncratic liver toxicity has been reported in association with carprofen therapy. Although considered rare (~ 5 cases/10,000 dogs treated), toxicity occurs approximately 2–4 weeks after starting therapy and results in acute hepatic necrosis. Contraindications for the use of NSAIDs include gastrointestinal ulcers, underlying bleeding disorders, renal dysfunction, dehydration, concurrent liver dysfunction, and concurrent steroid therapy. NSAIDs have significant drug interactions with glucocorticoids (gastrointestinal ulceration is potentiated by glucocorticoids via inhibition of prostaglandin synthesis), benzodiazepines, salicylate containing herbs (meadowsweet or willow), gingko, garlic, ginger, ginseng, and aminoglycosides.

Clinical indications include musculoskeletal pain (chronic osteoarthritis, acute trauma or injury, or postoperative pain and inflammation). COX-2 selective inhibitors may have fewer gastrointestinal side effects and be safer in patients with bleeding disorders but are likely no advantage for patients with renal insufficiency. Pretreatment evaluation includes a baseline CBC and chemistry panel with electrolytes to rule out azotemia, anemia, or hepatic dysfunction (especially older patients). During therapy patients should be monitored for side effects including gastrointestinal upset, bleeding, and renal or liver dysfunction. Never use multiple NSAIDs concurrently and never use NSAIDs concurrently with glucocorticoids. Consider a minimum of a 7-day washout period between NSAIDs and either glucocorticoids or other NSAIDs.

COX nonselective NSAIDS are those that inhibit both COX-1 and COX-2. Examples include ketoprofen (Ketofen), used for perioperative analgesia in dogs as a single dose. Preferential COX-2 inhibitors include carprofen (Rimadyil), meloxicam (Metacam), and etodolac (Etogesic), approved for use in dogs with musculoskeletal pain. Due to less COX-1 inhibition, there is potentially less GI upset and ulceration and fewer effects on platelet function. COX-2 selective inhibitors have no effect on platelet function and a lower risk of gastric ulceration (although COX-2 inhibition may impair healing of preexisting ulcers). COX-2 selective inhibitors approved for use in dogs include deracoxib (Deramaxx) and firocoxib (Previcox®). Tepoxalin (Zubrin) is both a COX-1 and COX-2 inhibitor but also inhibits 5-lipoxygenase (LOX-5) and is approved for the treatment of osteoarthritis in dogs, although the clinical advantage remains unclear. Acetaminophen, due to its weak COX inhibition (COX-3), has no increased risk of gastric ulceration or platelet inhibition. There are no veterinary clinical indications for acetaminophen use, but when combined with codeine it is sometimes used to treat chronic cancer pain in dogs. Side effects include hepatotoxicity secondary to an overdose in dogs and methemoglobinemia in cats (acetaminophen is contraindicated in cats).

**Opioids**

Opioids act by limiting the input of nociceptive input into the CNS. Central opioid receptors are located in the brain and dorsal horn of the spinal cord, and peripheral opioid receptors are located in joint capsules, pleural membranes, and organ capsules. Opioids interact with one or more of the major opioid receptors (mu, sigma, kappa, or delta). The effect of any given opioid is dependent on its interaction with specific opioid receptors, the density of the receptor population, and the cell type in which receptors are located. Opioids are potent analgesics with a rapid onset
of action, and dependent on the type, may be reversible. Side effects include respiratory depression, bradycardia, panting, hypothermia, dysphoria and/or agitation (cats—hyperexcitability or agitation), ileus and constipation, urinary retention, and miosis.

**Full opioid agonists** provide analgesia for moderate to severe pain and are considered the gold standard for acute pain relief and the standard of care for any surgical procedures. Pure mu agonists include morphine, hydromorphone, oxymorphone, and fentanyl. Morphine has poor oral bioavailability; thus oral use is limited to a sustained-release formulation. Epidural morphine provides a localized and more intense effect in obtunding nociception without significantly affecting motor function. Morphine’s lipophilic structure enables diffusion through neuronal tissue, providing a high potency and long duration of analgesia. Indications for epidural morphine include orthopedic surgery of hind limb or caesarian section. Contraindications include trauma over the pelvic region, septicemia, coagulopathy, CNS disease, skin infections over the site of injection, hypovolemic shock, and severe obesity. Side effects may include hypotension, neurological complications, pruritus, urinary retention, and epidural technical failure. Oxymorphone is preferred in cats to hydromorphone, as hydromorphone may cause hyperthermia in cats; in one study 60% of cats treated with hydromorphone became hyperthermic, with body temperatures reaching as high as 107°F. Fentanyl is the analgesic choice in critical patients and for painful procedures. Due to fentanyl’s more lipophilic structure, CNS concentrations follow plasma concentrations. Fentanyl is short-acting; thus administration is limited to a constant rate infusion or transdermal delivery. Transdermal delivery of fentanyl provides systemic absorption, although there is significant individual variation in systemic drug levels. Absorption is dependent on the site of application, skin temperature, and blood flow. The use of transdermal fentanyl is a concern for human exposure, accidental ingestion, and public health risk. CRI delivery maintains effective plasma concentrations for pain relief. Other mu agonists include tramadol and methadone. Tramadol is a weak mu agonist, with marked effect on serotonergic ([+] tramadol inhibits serotonin reuptake) and noradrenergic systems ([–] tramadol inhibits norepinephrine reuptake). The metabolite (+) O-desmethyltramadol has the greatest affinity for the mu receptor. Tramadol has 10% of the analgesic potency of morphine, with little effect on respiratory, cardiovascular, and gastrointestinal systems. Indications include neuropathic pain, musculoskeletal pain, mixed nociceptive-neuropathic pain, and acute and chronic pain. Consider dose reduction in patients with renal or liver disease. Use is contraindicated in patients with a seizure history (it lowers the seizure threshold) and concurrently with other serotoninergic drugs, including tricyclic antidepressants (clomipramine), selective serotonin reuptake inhibitors (fluoxetine), selective norepinephrine reuptake inhibitors (venlafaxine), and St. John’s wort. Methadone is a synthetic opioid, selective for the mu receptor. It has questionable oral bioavailability, but parenteral methadone may be a good choice in a sedation protocol for an ultrasound exam when used with dexmedetomidine due to less panting.

**Partial opioid agonists**, partial mu agonist and kappa agonist, bind the same receptors as full agonists but have a less profound effect (provide mild to moderate pain relief) and fewer opioid type adverse effects (respiratory, cardiovascular, GI). A disadvantage of partial agonists is their ceiling effect, a maximal effect reached at the upper end of the dose range; thus, if pain is severe or analgesia is inadequate, additional doses are unlikely to be effective. Buprenorphine is considered a better analgesic in cats relative to other species, and transmucosal administration has good systemic absorption. Buprenorphine, due to high receptor affinity, is more difficult to reverse and has a duration of 8 hours. Transdermal buprenorphine patches have no systemic absorption in animals.

**Opioid agonist-antagonist** effects are receptor dependent; it functions as an agonist at one receptor (analgesic effect) and an antagonist at a different receptor (less pronounced or no effect). Butorphanol is a kappa agonist and mu antagonist. Butorphanol is used to treat mild to moderate pain, with short duration of action (1 to 2 hours), but it also can be used to reverse sedation and respiratory depression from mu agonists. Complete reversal of analgesia does not occur due to kappa agonist effects and additive analgesia with the mu agonist. Oral bioavailability is decreased by 10 to 30% due to significant first pass hepatic metabolism, and butorphanol exhibits a ceiling effect.

**Opioid antagonists** bind the same opioid receptors but have no effect, competitively displacing the agonist from the receptor and thus reversing the agonist’s effect. Naloxone is a pure antagonist used to reverse CNS depression, respiratory depression, and bradycardia associated with full opioid agonists. Low dose naloxone is titrated slowly IV to reverse CNS depression without affecting analgesia. Side effects include excitement, delirium, aggression, and hyperalgesia. Naloxone’s duration of action is approximately 20–30 minutes.
Local Analgesia

Local anesthetics block nerve conduction by binding within the transmembrane pore of sodium channels in nervous tissue, preventing sodium permeability, cellular depolarization, and generation of an action potential, impacting both sensory and motor neurotransmission. Pain signal initiation and transmission is blocked from peripheral nerves to the CNS, decreasing pain perception. Use is limited to tissues adjacent to the site of application or injection, providing local analgesia. Structurally local anesthetics have a hydrophilic and hydrophobic domain, and those linked by amide linkages are referred to as amide-type (lidocaine and bupivacaine). The base form is needed to penetrate the cellular lipid membrane, and the cationic form predominates at physiological pH. Analgesic effect is related to volume and the concentration of the drug. Metabolism is by the liver via conjugation to glucuronic acid (thus use is more problematic in cats). Indications include surgical procedures (preemptive analgesia and post-op pain management), local nerve blocks for brief painful procedures, intra-articular analgesia, digital or brachial plexus nerve blocks, and intercostal or pleural analgesia. Epidural use lowers drug concentrations and provides analgesia without motor deficits (bupivacaine). Side effects include CNS (muscle twitching, tremors, and seizures), cardiovascular (bradycardia, hypotension, and cardiac arrest), and allergic immune-mediated reactions.

Lidocaine provides good all-around local analgesia with a rapid onset (minutes) and moderate duration (1–2 hours). Duration can be prolonged by the addition of epinephrine, decreasing vascular uptake and systemic toxicity. Duration is shortened by the addition of bicarbonate by decreasing interaction with sodium channels, but it increases the rate of onset and reduces the string of injection. It is metabolized rapidly by the liver. Cats, due to their lack of glucuronidation, are more sensitive to lidocaine toxicity than dogs. It can be used topically as a eutectic mixture—lidocaine (2.5%) prilocaine (2.5%) (EMLA)—to treat acute pain (blood draw). Transdermal delivery is available as a lidocaine patch, Lidoderm (5% lidocaine, nonsterile), providing dermal absorption with a low rate of systemic absorption. Transdermal lidocaine provides analgesia (small non-myelinated fibers) without blocking all sensory and motor input, and used in treating neuropathic pain. In dogs, clinical usefulness is 3–5 days, but use in cats warrants further investigation. Lidocaine used systemically in combination with morphine-lidocaine-ketamine (MLK) as a CRI provides balanced analgesia for dogs. MLK takes advantage of synergism with multiple receptor activation. Ketamine attenuates and reverses morphine tolerance, thus producing an opioid-sparing effect with superior analgesia compared to either drug alone. Ketamine also decreases wide-up phenomenon “chronic pain” (untreated pain worsens due to increased recruitment and lower threshold of depolarization of C fibers [slow pain receptors]). Chronic pain involves upregulation of NMDA receptors, resulting in an exaggerated response to painful stimuli.

Bupivacaine is a popular local anesthetic in veterinary medicine, with a longer onset and prolonged duration of action relative to lidocaine (higher protein binding, 99%). Bupivacaine blocks conduction in sensory nerves more effectively than motor fibers and is more cardiotoxic (arrhythmias and decreased cardiac output) due to slower dissociation from the site of action.

Others

Leflunomide (Arava®) inhibits de novo pyrimidine biosynthesis via its active metabolite (malononitriloamide), a selective pyrimidine synthesis inhibitor. Leflunomide is also considered an immunomodulator by inhibition of cytokine and growth factor receptors associated with tyrosine kinase activity. Immunomodulatory mechanisms include inhibition of B and T cell proliferation, immunoglobulin production, and pro-inflammatory cytokines, augmentation of immunosuppressive cytokines (TGF-β), interference with cell adhesion, and COX-2 inhibition. Indications include immune-mediated polyarthritis, osteoarthritis, and a role in other immunosuppressive diseases. Side effects include lethargy, gastrointestinal upset (nausea, vomiting, diarrhea) that is transient and responds to dose reduction, and elevated liver enzymes (less than a twofold increase and responds to dose reduction), and its use is not recommended during pregnancy.

Gabapentin is a structural analog of GABA and is an NMDA receptor antagonist. Indications are limited to some forms of chronic pain, including neuropathic “wind-up” pain. Side effects (not well established in veterinary medicine) include sedation. Efficacy is unpredictable in both humans and animals, and it has overall very limited use in veterinary medicine, especially long-term use. Use with caution in patients with renal dysfunction.

Clinical Considerations

Multimodal analgesia is recommended to provide balanced analgesia while minimizing individual drug doses and potential adverse effects. Clinical conditions that require special consideration include geriatric patients, critically ill patients, trauma patients (cranial trauma), surgical patients, and chronic pain management in cancer patients. Prior to
treating any painful patient, pain must be identified or recognized and classified. Consideration should be given to
the type and duration of pain that is most likely present, including acute versus chronic pain, neuromuscular versus
neuropathic versus viscera versus wind up, and the anticipated duration of the pain. Other important parameters to
consider for each patient include age, identifying any underlying systemic problems, concurrent medications, and
contraindications.