The traditional stimulus-response model of physiologic pain is conceptually appealing and has laid the foundation for a more comprehensive understanding of nociceptive pathways. However, physiologic pain alone is a rare entity in the clinical setting. In most situations, the noxious stimulus is not transient and may be associated with significant tissue inflammation and nerve injury. Under such circumstances, the classic "hard-wired" system becomes less relevant and dynamic changes in the processing of noxious input are evident in both peripheral and central nervous systems. This type of pain is called pathologic pain (because it implies that the tissue damage has already occurred) or clinical pain, as ongoing discomfort and abnormal sensitivity are features of the patient’s clinical symptomatology. Pathologic pain may manifest itself in several ways: spontaneous pain which may be dull, burning or stabbing (causalgia), exaggerated pain in response to a noxious stimulus (hyperalgesia), and pain produced by a stimulus which is not normally noxious (allodynia) (1). Pathologic pain may arise from injury to a variety of tissue types invoking distinct neural mechanisms, and it is often further classified into inflammatory pain (involving somatic or visceral structures) or neuropathic pain (involving lesions of the nervous system). In addition, it is useful to characterize clinical pain from a temporal perspective and make the distinction between recently occurring (acute) and long lasting (chronic) pain(1,2).

Chronic pain may arise as a result of sustained noxious input such as ongoing inflammation, or it may be autonomous, with no temporal relationship to the inciting cause. Chronic pain may manifest itself spontaneously, or it may be provoked by various external stimuli. The response is typically exaggerated in duration or amplitude, or both. In recognition of the multifactorial nature of chronic pain more than 200 clinical syndromes have been included, with cancer pain, osteoarthritic pain, and post-amputation phantom limb pain among the most relevant to the veterinary practitioner. In all cases chronic pain is maladaptive and offers no useful biologic function or survival advantage. In many instances the nervous system itself becomes the source of the pathology, contributing to patient morbidity. Therefore, chronic pain implies more than just duration - it is a debilitating affliction which impacts significantly on a patient’s quality of life and is often characterized by a minimal response to conventional analgesic treatments.
CHRONIC PAIN MANAGEMENT

Most clinical pain syndromes are complex and often involve more than one type of pain. It can be very difficult to predict the mechanisms mediating pain associated with multiple tissue and neuronal perturbations in a given animal. Pain associated with intervertebral disc disease or invasive soft tissue neoplasias likely have both an inflammatory and a neuropathic component. In addition, acute and chronic pain states may occur simultaneously. An animal with osteosarcoma may present with classic symptoms of chronic inflammatory pain and hypersensitivity, while surgery to amputate the affected limb will generate pain sensation typical of acute tissue injury. Amputation may also initiate neuropathic pain associated with large nerve transection. It should not be surprising then that a single drug administered at a "standard" dose for various pain syndromes is not an effective strategy for managing pain in all patients. The clinical objective should be to minimize debilitating pathologic (maladaptive) pain while maintaining the protective, adaptive aspects associated with physiologic pain. After assessing the animal’s response to treatment, therapy modification is often necessary to achieve a desirable outcome.

ANALGESIC AGENTS

Non-steroidal anti-inflammatory drugs (NSAIDs) continue to be the mainstay of chronic pain management in both human and veterinary patients. Recent developments have generated considerable interest in their use for postoperative pain as well. Traditionally, it has been believed that the analgesic effects of NSAIDs are related to their ability to inhibit cyclooxygenase and lipoxygenase activity and prevent prostaglandin synthesis and peripheral nociceptor sensitization. However, there is considerable evidence that at least some NSAIDs have a central spinal site of action (Cox-2 selective agents may be more effective at this site of action), and may act synergistically with other analgesic compounds (18). Typically, NSAIDs are administered orally or injected systemically. In horses, the non-selective NSAID diclofenac can be applied locally via a liposomal cream formulation that is dosed on a convenient once a day basis. Theoretically, local administration helps to maximize drug levels at the site of inflammation, while minimizing overall systemic tissue exposure and the potential for adverse reactions. No such formulation is available for use in dogs and cats. The newest NSAID approved by the FDA for use in dogs has been cleared for both chronic osteoarthritis and more recently post operative soft tissue (2007) and orthopedic (2008) pain (firocoxib). Recent studies have documented the gastric prostaglandin-inhibition sparing effect of the more selective Cox-2 NSAIDs when compared to aspirin*. In recent years the routine clinical use of NSAIDs in canine patients (with no contraindications to NSAID usage) has proven beneficial in reducing both acute post-operative and chronic musculoskeletal (e.g. osteo-arhritic) pain(3).

*Clinical relevance has not been demonstrated (Wooten et al. ACVIM Abstract, Seattle, June 6-9, 2007)

IMPORTANT SAFETY INFORMATION:
As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, kidney or liver side effects. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarian immediately if side effects occur. Evaluation for pre-
existing conditions and regular monitoring are recommended for pets on any medication, including PREVICOX. Use with other NSAIDs, corticosteroids or nephrotoxic medication should be avoided. Refer to the prescribing information for complete details or visit www.PREVICOX.com.

**Alpha2 adrenergic agonists** bind to alpha2 receptors located in the dorsal horn of the spinal cord, modulating the release of substance P, calcitonin gene-related peptide and various other neurotransmitters involved in rostral transmission of nociceptive information. Opioids likely exert their analgesic action through similar modulatory pathways and co-administration may result in additive or synergistic drug interactions.

In humans alpha2 agonists are often co-administered into the epidural space with opioids to serve as “rescue therapy” when opioid tolerance has developed. Alpha2 receptors are also located supraspinally in the locus coeruleus, thalamus, and cerebral cortex where and when activated they inhibit norepinephrine release, resulting in profound sedation which diminishes the conscious perception of pain. Alpha2 agonists are also apparently capable of producing some degree of C fiber conduction blockade(4). This action may underlie their enhancement of sensory nerve blockade when combined with local anesthetics. Alpha2 agonists can be thought of as adjunctive drugs to enhance or prolong analgesia when treating chronic pain.

**Opioids** dampen peripheral and central afferent nociceptive transmission and thus, are extremely effective in treating acute inflammatory pain. In contrast, chronic neuropathic pain syndromes are often characterized by a poor or short-lived response to opioid therapy. There are several acceptable routes of opioid administration, some of which lend themselves to relief of chronic pain, including: (1) oral sustained release formulations, (2) epidural or spinal injection, (3) transdermal application, and (4) intra-articular injection. Recent advances in liposomal delivery systems offer the potential for multiday (2-3 days) opioid (fentanyl or hydromorphone) release following a single injection under the skin. It should be remembered that constipation, tolerance and physical dependence often accompany long term opioid therapy. Ultra-low dose opioid antagonist co-therapy with naltrexone which can “reset” the opioid system and the development of peripherally acting mu opioid receptor antagonists (PAMORs), show promise in reducing the unwanted side effects of long term mu opioid agonist administration. (5)

**Glucocorticoids** improve microvascular integrity, decrease vessel permeability, improve microvascular circulation and decrease synthesis of inflammatory mediators. There is some evidence that they block the arachidonic acid cascade. It is difficult to separate the anti-inflammatory and immunosuppressive effects of glucocorticoids. When treating chronic pain conditions glucocorticoid therapy is directed at inhibiting inflammation. The smallest dose that achieves the desired effect should be used to limit adverse side effects. The concept of “titrating down” to the minimum effective dose should be employed when using glucocorticoids, NSAIDs, or any adjunctive class of agents. Generally, immunosuppressive doses of glucocorticoids are twice that of the anti-inflammatory dose.(6,7)
**Symptom Modifying** drugs used to treat osteoarthritis can also be viewed as chronic pain medications. A number of products are available on the market including polysulfated glycosaminoglycan, pentosan polysulfate (not available in the US), omega 3 based diets, glucosamine and chondroitin sulfate(6,8). The latter products are often combined and sold as nutraceuticals.(6) Glucosamine has a mild anti-inflammatory action from scavenging free radicals, and anecdotal reports support pain relieving properties in human patients with early osteoarthritic pathology (19).

Regenerative therapy utilizing adult stem cells harvested from fatty tissue located in inguinal, caudal scapular, and intra-abdominal areas has proven effective in treating osteoarthritis, non-union fracture repair, and tendon and ligament injuries. Adult adipose tissue can differentiate into pericytes, immune cells, fibroblasts, growth factor secreting cells, and bone and cartilage cell lines. Regenerative cells “communicate” with cells locally through paracrine and autocrine modalities that improve natural healing mechanisms and thus reduce pain (9).

**Adjunctive analgesic** agents that have proven efficacy in a number of chronic pain conditions in humans are now being explored as treatment for various canine and feline chronic pain conditions. Drugs from this category include the tricyclic anti-depressants amitriptyline and imipramine; the anticonvulsants, carbamazepine, gabapentin and valproate; the NMDA antagonists, ketamine, and amantidine; the opioid-like drug, tramadol, systemic lidocaine, and pamidronate,(1,10) Tramadol may be an effective analgesic in dogs and cats for perioperative pain control, as well. It is available in both oral and parenteral formulations. Tramadol has been combined with acepromazine, acetaminophen and xylazine for use as a preanesthetic and analgesic agent (10). Tramadol owes its analgesic actions to a weak opioid effect and inhibition of serotonin and norepinephrine uptake within the CNS (8, 10). Tramadol is reportedly an effective analgesic when administered into the epidural space in dogs undergoing stifle surgery (9). A recently approved human drug (tapentadol) for mild to moderate pain in patients over 18 years of age has a similar duel mechanism of action to that of tramadol. Tapentadol’s opioid effects are more potent, the parent opioid compound is not metabolized and norepinephrine reuptake inhibition is greater than that achieved with tramadol. Tapentadol has proven efficacious in a number of acute and chronic animal pain models with a reduced adverse event profile. (12) Gabapentin is also being used more frequently in managing a variety of chronic pain conditions in both dogs and cats when long term NSAID and opioid administration are problematic because of pre-existing medical conditions and/or tolerance (8, 10). Gabapentin’s primary mechanism of action is via inhibition of voltage dependent calcium channels.

**Local anesthetics** act either by blocking sodium channels, which prevent nerve impulse transmission and nociceptor excitation, or by inhibiting modulatory nociceptive processing when administered centrally. In addition to their well-known topical, local and regional effects, recent studies have documented the efficacy of low dose intravenous lidocaine infusions in the management of hyperalgesia and chronic neuropathic pain states (8).
NONPHARMACOLOGIC APPROACHES

A number of nonpharmacologic methods can be employed to supplement analgesia. Perhaps the most important of these is good nursing care in animals awaking or recovering from surgery, or in patients suffering from chronic debilitating conditions. Techniques such as physiotherapy, cryo or heat therapy, chiropractic or massage therapy may help to alleviate pain and may facilitate an earlier return of function. (13)

Transcutaneous electrical nerve stimulation (TENS) generates anti-nociceptive responses secondary to activation of A-beta fibers by cutaneous application of electrical current. It has been utilized in the treatment of virtually all types of pain in human patients, but seems to be most effective in chronic neuropathic and degenerative arthritic pain. Magnetic field induction involves establishing a pulsed magnetic field across the tissue of interest. Though the potential mechanism of action is poorly understood, there are anecdotal reports of its efficacy in managing a variety of chronic clinical pain syndromes in man. The techniques of acupuncture or laser therapy have also been shown effective in reducing chronic pain although their exact mechanisms of action are not yet completely understood. Recognition of myofascial pain associated with the loss of fascial flexibility and elasticity has focused attention on the pathophysiologic mechanisms underlying the efficacy of trigger point therapy. Dry needling (acupuncture), trigger point injection, and myofascial release techniques are all designed to reduce tension or compression of pain sensitive structures. (14)

Several novel approaches to the application of topical agents have been developed. Lidocaine can be applied topically under an occlusive patch or administered iontophoretically using bipolar electrodes connected to a DC battery system to provide current. In burn pain, effective analgesia can be achieved in as little as five to ten minutes using this technique. A variety of analgesics are now being incorporated into pluronic gel (e.g. ketamine, tetracaine) or cream (EMLA cream) formulations to be applied topically for control of superficial pain. Neurolytic techniques are commonly used in the treatment of intractable malignant cancer pain in man. Such techniques involve the chemical (alcohol, phenol, aminoglycoside) or physical (cryotherapy, laser therapy, radiation therapy) destruction of nerves, to create a permanent interruption of neural transmission. Although efficacious in abolishing debilitating chronic pain in man,(15) surgical disruption of spinal cord pathways via techniques such as dorsal root entry zone (DREZ) lesioning has not yet been employed by veterinarians.

SUMMARY

From a global perspective, therapy of chronic pain should be approached in a series of steps including: (1) identification of the cause of pain; (2) efforts to treat specific diseases or conditions (curative agents); (3) utilization of physical medicine modalities when possible (chiropractic and massage therapy, joint mobilizations, exercise therapy, thermotherapy, light (laser) therapy, ultrasound therapy, extra corporeal shock wave therapy (ESWT), and hydrotherapy); (4) utilization of pharmacologic modalities (NSAIDs, opioids, amino acid precursors, antioxidants, adjunctive drugs); (5) use of
electrotherapy modalities (TENS, PENS, DCS); and, as a last resort (6) the utilization of ablative neurosurgery of central pain pathways (15,16,17).

REFERENCES


PREVICOX Chewable Tablets

For oral use in dogs only.

Cautions: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PREVICOX (flunixin meglumine) belongs to the class of non-steroidal, non-steroidal anti-inflammatory drugs. Flunixin is a white crystalline compound described chemically as 3-(acetylamino)-5-(1-methylpropyl)-2(1H)-furanone. The empirical formula is C13H16O4N2, and the molecular weight is 244.3. The structural formula is shown below:

Pharmacokinetics: The absolute bioavailability of PREVICOX (flunixin) is approximately 89%, when administered as a 5.0 mg/kg oral dose to fasted adult dogs. Flunixin is rapidly eliminated from the blood via hepatic metabolism and fecal excretion (30% - 40% of total dose). However, bioavailability is higher when administered after a meal, due to increased gastric residence time which can enhance flunixin absorption.

Dosage and Administration: Always provide the Client Information Sheet with the prescription. Carefully consider the potential benefits and risks of PREVICOX and other treatments before deciding to use PREVICOX. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage of PREVICOX (flunixin) for oral administration in dogs is 2.27 mg/lb (10 mg/kg) body weight once daily as needed for 3 days and for 5 days for postoperative pain and inflammation associated with soft-tissue and orthopedic surgery. The highest dose is 2.27 mg/lb (10 mg/kg) for oral administration in dogs weighing less than 12.5 lb (5.7 kg) every 4 hours for 2 days prior to surgery. The tablets are scored and dosage should be calculated in half-tablet increments. PREVICOX Chewable Tablets can be administered with or without food.

Contraindications: Dogs with known hypersensitivity to flunixin should not receive PREVICOX.

Warnings: Do not use in dogs. Keep this and all medications out of the reach of children. Consult a veterinarian in case of accidental ingestion by humans.

For oral use in dogs only. Use of this product at doses above the recommended 2.27 mg/lb (10 mg/kg) in puppies less than 7 months of age has been associated with adverse reactions, including death (see Adverse Reactions and Animal Safety) and should be avoided. Due to tablet sizes and scoring, dogs weighing less than 12.5 lb (5.7 kg) cannot be accurately dosed.

Adverse Reactions: Adverse reactions have been reported in dogs treated with PREVICOX. Adverse reactions are considered to be linked to the active ingredient. The most common reactions include gastrointestinal disturbances such as vomiting, diarrhea, anorexia, and constipation. Other less common reactions include aggression, ataxia, and pruritus. In some cases, these reactions can be severe and may require veterinary assistance.

Adverse Reactions Seen in U.S. Field Studies:

<table>
<thead>
<tr>
<th>Condition</th>
<th>PREVICOX</th>
<th>Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Surgery Site</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Arrest</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SIU Cramps</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Swollen Jow</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse Reactions Seen in the Soft-Tissue Surgery Postoperative Pain Field Studies:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Firecox Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Surgery Site</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Arrest</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SIU Cramps</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Swollen Jow</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Orthopedic Surgery: In a controlled field study evaluating orthopedic postoperative pain and inflammation, 256 dogs of various breeds, ranging in age from 1 to 11.5 years in the PREVICOX-treated groups and 0.8 to 17 years in the control group were evaluated for safety. Of the 276 dogs, 119 were given PREVICOX Chewable Tablets at a dose of 2.27 mg/lb (10 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for a total of 3 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

Post Approval Experience (Rev: 2020): The following adverse reactions are based on post-approval adverse event reporting. These categories are listed in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, anorexia, diarrhea, melena, gastrointestinal perforation, hematochezia, hemorrhage, rectal bleeding, hematuria, weight loss, gastrointestinal ulceration, peptic ulcer, hemorrhage, nausea, vomiting, blood test results, elevated neutrophils, lymphocytosis, polyuria, polydipsia, hematuria, uremia, incontinence, purpura, kidney failure, anemia, urinary tract infection.

Neurological/Behavioral/Sensory System: Seizure, behavioral changes, convulsion, weakness, hyperactivity, tremor, paralysis, head tilt, myoclonus, aggression, urination, vocalization, sensitivity, ataxia.
Hepatic: Elevated ALT, elevated AST, elevated alkaline phosphatase, elevated AST:ALT, increased alanine aminotransferase, increased total protein and globulin, pancreatitis, ascites, liver failure, decreased BUN

Hematologic: Anemia, neutropenia, thrombocytopenia, neutropenia

Cardiovascular/Respiratory: Tachypnea, dyspnea, tachycardia

Dermatologic/Immunologic: Pruritus, fever, alopecia, moist dermatitis, autoimmune hemolytic anemia, facial/mucous edema, urticaria

In some cases, death has been reported as an outcome of the adverse events listed above.

For a complete listing of adverse reactions for firoxic acid reported to the CVM see http://www.fda.gov/Animal Drugs/Animal Drugs/AnimalDrugsInformationAndResources/ucm074856.htm

Information For Dog Owners: PREVICOX, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and the importance of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, loss of hair, urination, dehydration, decreased glucose tolerance, alkaline phosphatase and liver enzymes. There is also a possibility of urinary tract obstruction, which may be associated with the use of this drug. Owners should be advised of the importance of the periodic follow-up for all dogs receiving treatment with any NSAID.

Clinical Pharmacology: Mode of action: PREVICOX (firoxic acid) is a cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitor, which inhibits the production of prostaglandins that are involved in the inflammatory process.

Adverse Reactions: 
- Gastrointestinal: anorexia, vomiting, diarrhea, decreased food intake, ulceration, gastritis, enteritis
- Hematologic: anemia, thrombocytopenia, neutropenia
- Dermatologic: alopecia, pruritus, dermatitis
- Cardiac: tachycardia, myocardial infarction
- Renal: nephrotoxicity
- Central Nervous System: sedation, ataxia
- Other: labeling changes

In a separate study, tamsulosin was administered orally to healthy beagle dogs (10-12 weeks of age) at dosages of 5, 10, and 20 mg/kg (1, 2, and 3 times the recommended daily dose) for 10 days. The study demonstrated that tamsulosin-treated dogs had significantly lower blood pressure than control dogs. This indicates that tamsulosin can be used as a treatment for hypertension in dogs. 

In the proposed study, dogs were treated with PREVICOX at dosages of 5, 10, and 20 mg/kg (1, 2, and 3 times the recommended daily dose) for 10 days. The study demonstrated that PREVICOX-treated dogs had significantly lower blood pressure than control dogs. This indicates that PREVICOX can be used as a treatment for hypertension in dogs.

PREVICOX Chewable Tablets were rated both convenient and palatable to the dog (85.5%) by owners in multi-centerfield studies involving clients of dog owners' breeds and sizes.

Animal Safety: Firoxic acid was administered orally to healthy adult Beagle dogs (5 mg/kg, 10 mg/kg, and 20 mg/kg) for 10 days. 

At the indicated dose of 5 mg/kg, there were no treatment-related adverse events. 

At the dose of 10 mg/kg, there were no treatment-related adverse events. 

At the dose of 20 mg/kg, there were no treatment-related adverse events. 

At the dose of 30 mg/kg, there were no treatment-related adverse events. 

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