BEYOND NSAIDS: WHAT CAN WE DO FOR CHRONIC PAIN?  ANESTHESIA
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Acute Versus Chronic Pain
Acute and chronic pain differ in ways other than their duration. Acute pain typically follows some tissue insult such as surgery or trauma. The pain resolves as the injury heals. Acute pain lasts less than one month and tends to be self-limiting. Acute pain also tends to be very responsive to conventional drug therapy, including NSAIDs, alpha-2 agonists, and opioids. Chronic pain lasts longer than a month and can exist even after the original injury has healed. Chronic pain may exist in the absence of the inciting stimulus as a result of pathophysiologic changes in the central nervous system. Pain receptors in the spinal cord develop neurologic memory, so that the receptors themselves may become the source of the pain long after the original pain stimulus is gone. Chronic pain from some causes (e.g., cancer) may be difficult to treat and poorly responsive to conventional analgesic therapy. Unfortunately, therapy for chronic pain may be palliative at best and may require multiple pharmacologic components and treatment modalities (i.e., various analgesic drugs, acupuncture, massage, physical therapy, weight control, etc.). Left untreated, chronic pain can radically alter an animal’s quality of life and result in behavioral changes that ultimately lead to euthanasia of the pet.

Osteoarthritis (OA) is overwhelmingly the main cause of chronic pain in dogs and cats. Based on the population of aged dogs in the United States, it is estimated that 1 in 5 adult dogs are likely to have some form of OA. Fortunately, chronic pain due to OA—if diagnosed early—is often responsive to weight loss, controlled exercise, and non-steroidal anti-inflammatory drugs (NSAID) and/or disease modifying agents (e.g., chondroitin sulfate). If diagnosed after the disease has become moderate to severe, multimodal therapy will probably be required, and even aggressive therapy may not completely eliminate all pain. Thus, it is imperative that we emphasize the signs of OA to our clients and to our staff members who may be involved in patient physical examinations. OA is most often seen in large-breed dogs (over 50 lbs), patients older than 7 years of age, patients having a history of being very active, and overweight patients (thus, weight loss is an important part of therapy).

Cancer is the second most common cause of chronic pain in animals. Although geriatric pets are most frequently affected, cancer can strike at any age. Patients will almost always require a multimodal approach to pain therapy and may also require a variety of non-pharmacologic analgesic therapies (e.g., acupuncture) as well as multiple analgesic adjunctive medications (e.g., NMDA antagonists).

Treatment of Chronic Pain
As stated, treatment of chronic pain is not always easy and often requires a combination of therapies. This combination may include multiple pharmaceutical agents, pharmaceutical agents plus non-pharmacologic therapy (e.g., acupuncture, massage, etc.), or both. Often, finding an effective treatment takes time and must proceed on a “trial and error” basis. It is important to remember—and important to explain to the client—that chronic pain is a very individual disease, and treatment protocols almost always require modification for each individual patient. Treatment of chronic pain is most effective when the clinic staff operates as a pain management team. However, a pain management strategy for treating chronic pain will not work unless the pet’s owner is also a part of the team. The owner should be educated as to the underlying condition that causes pain, as well as to the effects and side effects of the analgesic therapy. Furthermore, the owner must be committed to long-term therapy and to assessing the extent of the pet’s pain and relief of pain from analgesics. Various pain assessment forms are available for the owner to use at home. Also, owners should be advised that adequate pain control involves more than just treatment of the pain itself. Weight loss is extremely important in overweight patients, and alteration of the pet’s environment (e.g., eliminate need for pet to climb stairs, cover slick floors with mats or rugs to provide better footing, etc.) and activity level (e.g., more controlled activity like leash walking is often the best for a pet in pain) are often part of the treatment plan.

Analgesic Drugs
Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment of chronic pain. This protocol has been developed with good reason since most forms of chronic pain do have an inflammatory component. However, what options are available when the patient is unable to take NSAIDs or, more commonly, when the pain advances to a state that is uncontrollable by NSAIDs alone? In that instance, opioids, N-methyl-D-aspartate (NMDA) antagonists, and novel drugs like gabapentin should all be considered as potential therapies. In addition (but outside the scope of this presentation), non-pharmacologic therapies (e.g., acupuncture, massage, physical therapy, TENS,
etc.) should be strongly considered for these patients. Dosages for drugs used to treat chronic pain, along with considerations for the use of the drugs, are listed in Table 1.

Opioids

Tramadol is probably the most commonly used opioid for treatment of chronic pain in veterinary patients. Partly this is due to the fact that tramadol is not a DEA-scheduled drug. Tramadol is a centrally acting analgesic drug that is structurally related to both codeine and morphine and does have some opioid effects. However, tramadol also inhibits both serotonin and norepinephrine uptake. These varied activities are complementary and synergistic for analgesia and have led to the classification of tramadol by the US FDA as a “nontraditional centrally acting analgesic.” However, tramadol provides analgesia that is moderate at best and should be used as part of a multimodal protocol rather than as a stand-alone drug. This is further evidenced by the fact that absorption of the drug is highly variable in dogs, and it is not possible to predict which dogs might absorb the drug poorly, resulting in inadequate analgesia for that patient. In dogs, the systemic availability following 11 mg/kg of orally administered tramadol was 65 ± 38% and the half-life (t½) was 1.71 ± 0.12 hrs (Kukanich & Papich 2004).

When compared to dogs, bioavailability was greater (93 ± 7%) and the t½ was longer (204 ± 8 mins) in cats following 5 mg/kg tramadol administered orally (Pypendop & Ilkew 2008; Papich & Bledsoe 2007). Furthermore, cats produced a significant concentration of the active M1 metabolite, which also has a long t½. Because M1 has been attributed to opioid-related effects, there may be more opioid-mediated effects from administration of oral tramadol in cats compared to dogs.

In humans, tramadol has been used to treat a variety of both acute and chronic pain syndromes, but the drug is generally recommended as part of a multimodal therapy protocol and is commonly combined with NSAIDs, either as two independent drugs or as a combination product like Ultracet®, which is a commercially available combination of tramadol and acetaminophen. In dogs, the highly variable bioavailability, short t½ and lack of appreciable M1 metabolite concentrations, would also suggest that tramadol is best used as part of a multimodal protocol. Although the use of tramadol for analgesia in dogs appears to be fairly widespread, a review of the literature in September 2008 yielded only one report of tramadol used for analgesia in this species (Mastrocinque & Fantoni 2003) and no published reports on the use of tramadol in cats. The anecdotal dose for the dog is 2–5 mg/kg BID to TID. The anecdotal dose for cats is lower, and the incidence of dysphoria in the cat is (anecdotally) fairly high.

Other opioids used in veterinary medicine include transdermal fentanyl, oral codeine, codeine + acetaminophen (DOGS ONLY), and oral morphine. These opioids are more potent than tramadol and should be considered anytime that pain is severe or when pain has advanced beyond the point that it can be controlled by tramadol. These opioids are DEA scheduled (fentanyl, codeine, and morphine are Class II; codeine + acetaminophen is Class III) and have a greater potential to cause side effects (primarily sedation, nausea and, eventually, constipation) than tramadol but are more likely to control severe pain.

Amantadine

Amantadine is an antiviral drug that was approved by the Food and Drug Administration in 1964 for the treatment of influenza virus A in adult humans. Since that time, a variety of uses for amantadine have come to light, including reduction of symptoms of Parkinson’s disease and control of some pain syndromes. Pain relief is mediated by antagonism of N-methyl-D-aspartate (NMDA) receptors. In humans, the drug is well absorbed and widely distributed following oral administration. Elimination is primarily by renal clearance of unchanged drug. The pharmacokinetics of amantadine have been described in the horse but not in other veterinary species. In the horse, the pharmacokinetic report was in reference to the drug being used to treat equine influenza. In humans, the NMDA-receptor antagonists are being extensively researched and have been used for treatment of acute, chronic, and “specialized” (e.g., neuropathic and phantom limb) pain conditions, as well as for relief of symptoms of Parkinson’s and Alzheimer’s disease. Newer NMDA-receptor antagonists (e.g., memantine) are available. The role of amantadine in pain management has been reported in dogs by Lascelles et al (2008). Effective pain control was achieved when amantadine was combined with an NSAID and dosed at 5 mg/kg orally for 21 days. A literature search in September 2008 yielded no other veterinary publications describing the use of amantadine for analgesia. Amantadine has a variety of uses in chronic pain, and scenarios for addition of amantadine include:
• Anytime pain of “wind-up” could be an issue
• NSAIDs suddenly “not working” after controlling pain long-term
• Any long-standing untreated pain
• Moderate to severe cancer pain

Gabapentin
Gabapentin is commonly used to control seizures in both human and veterinary patients. In addition to the antiseizure activity, gabapentin has been shown to be effective in treating a variety of chronic pain conditions (including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headaches) in humans. Although both gabapentin and pregabalin are structural analogs of GABA, their mechanism of action is not mediated through GABA, and in fact the mechanism is not completely understood. Multiple mechanisms have been proposed for the action of gabapentin and pregabalin, but the current leading theory is that the drugs cause inhibition of presynaptic calcium currents via high-voltage-activated calcium channels containing the alpha-2-delta-1 subunit. This inhibition leads to reduced presynaptic neurotransmitter release and attenuation of postsynaptic excitability.

Although neither research manuscripts nor case reports are available regarding the use of gabapentin in dogs and cats, many practitioners are using the drug for control of various pain syndromes. The dosage generally ranges from 1–10 mg/kg PO BID to TID, but dosages as high as 30 mg/kg have been anecdotally reported. Generally, gabapentin therapy is initiated at 3–5 mg/kg PO BID and dosages increased as necessary. The most common side effect is sedation, and the dose of gabapentin should be reduced in patients that become sedated. Gradually increasing the dose over time generally eliminates the chance of sedation. If the patient is to be removed from gabapentin therapy (e.g., the patient is “cured” or the gabapentin is not working), the drug should be gradually withdrawn over a period of one to three weeks (depending on the duration of therapy) to prevent rebound hyperalgesia. Gabapentin has a variety of uses in chronic pain, and scenarios for addition of gabapentin should include:

• Anytime pain may be “neuropathic”
• All patients with painful backs/necks that have presented in moderate to severe pain
• All patients with painful backs/necks that have not resolved with NSAIDs or steroids
• All patients post back/neck surgery
• Any patient with difficult to diagnose, difficult to characterize pain
• Any patient with known nerve damage

Other Drugs
Because chronic pain is so difficult to treat, new drugs—or new applications for old drugs—are continually being investigated. Currently, other drugs to consider for treatment of chronic pain include antidepressant drugs (e.g., the tricyclic antidepressants), bone strengthening drugs like the bisphosphonates, and newer generations of currently used drugs like pregabalin (newer generation of gabapentin).

Some Common Scenarios with Treatment Recommendations (see Table 1 for dosing information):

1. A patient with mild OA has been on a NSAID for a week and the NSAID isn’t working to control pain.
   • Solution: Try another NSAID. Individual sensitivity exists in animals just like it exists in human beings. ALL NSAIDs work globally, but each individual may respond better to one NSAID than to another.

2. A patient with mild OA has been on a NSAID for an extended duration of time and the NSAID was controlling pain adequately until recently. Now, despite the fact that the disease doesn’t seem to be worsening, the patient is fairly painful.
   • Solution: Add amantadine to the current therapy. The most common explanation for this scenario is that the NMDA receptors in the dorsal horn of the spinal cord have become hypersensitized and are contributing to the sensation of pain in this patient. The NSAID should remain as part of the analgesic therapy for the inflammatory component of OA. The amantadine is an NMDA-receptor antagonist and is added to address that particular source of pain.
3. A patient with moderate OA or cancer pain is painful even on a NSAID.
   - Solution: Add tramadol (or another opioid) to the NSAID, either on a continuous basis or as needed basis. The opioids in cancer patients are generally administered on a continuous basis.

4. A patient with disc herniation is very painful but is not a candidate for surgery.
   - Solution: Add gabapentin to the NSAID (or steroid) treatment and use tramadol (or another opioid) either as continuous therapy or on an as needed basis.

Table 1. Dosages for drugs other than NSAIDs used to treat chronic pain in dogs and cats*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog Dosage</th>
<th>Cat Dosage</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>OPIOIDS</strong></td>
<td></td>
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<td>Chronic opioid use may cause constipation.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2–5 mg/kg PO BID-TID</td>
<td>Unknown. Probably 1–2 mg/kg BID</td>
<td>Tramadol is an “opioid like” drug that has other mechanisms of action. The pharmacokinetics in the dog are somewhat erratic, so the drug is best used as multimodal therapy with NSAIDs or other analgesic drugs.</td>
</tr>
<tr>
<td>Oral morphine (10, 15, 30 mg tablets)</td>
<td>0.5–4 mg/kg PO TID-QID</td>
<td>0.25–1.0 mg/kg PO TID-QID</td>
<td>Higher doses may induce sedation or dysphoria. Nausea and vomiting may also occur, but tolerance generally develops within 2 weeks following therapy initiation.</td>
</tr>
<tr>
<td>Sustained release oral morphine (15, 30, 60, 100, 200mg tablets)</td>
<td>0.5–4 mg/kg PO BID-QID</td>
<td>Difficult to dose due to size of tablets (tablets should not be scored).</td>
<td>Higher doses may induce sedation or dysphoria. Increase the frequency of administration prior to increasing dose if duration is not long enough.</td>
</tr>
<tr>
<td>Codeine (30 or 60 mg) plus acetaminophen (300 mg)</td>
<td>1–2 mg/kg (codeine) PO q 8–12 hrs</td>
<td>TOXIC TO CATS—DO NOT USE</td>
<td>Multimodal therapy improves analgesia over either drug used alone.</td>
</tr>
<tr>
<td>Transdermal fentanyl (25, 50, 75, 100 µg/hr patches)</td>
<td>3–5 ug/kg/hr</td>
<td>3–5 ug/kg/hr</td>
<td>May induce sedation or dysphoria. Addition of NSAID may improve analgesia.</td>
</tr>
<tr>
<td>Buprenorphine (0.3 mg/ml injectable)</td>
<td>0.01–0.03 mg/kg SC, IM, IV</td>
<td>0.01–0.02 mg/kg SC, IM, IV or buccal</td>
<td>More likely to be useful for chronic pain in cats due to effective oral dosing.</td>
</tr>
<tr>
<td><strong>OTHER DRUGS</strong></td>
<td></td>
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</tr>
<tr>
<td>Amantadine (100 mg capsule, 10 mg/ml liquid)</td>
<td>2–5 mg/kg PO SID</td>
<td>2–5 mg/kg PO SID</td>
<td>Does not provide analgesia directly but helps prevent/treat wind-up due to NMDA receptor antagonist activity.</td>
</tr>
<tr>
<td>Gabapentin (100, 300, 400 mg tablets)</td>
<td>1.25–10 mg/kg PO SID or BID; to 30 mg/kg SID (start with 3–5mg/kg)</td>
<td>1.25–10 mg/kg PO SID or BID; up to 30 mg/kg SID (start with 3–5 mg/kg)</td>
<td>May not provide analgesia directly but may help control abnormal neural processing in patients with peripheral and central neuropathic and chronic pain.</td>
</tr>
<tr>
<td>Glucosamine (500 mg)/Sodium Chondroitin Sulfate (400 mg) (Other concentrations are available)</td>
<td>For example, 13–15 mg/kg chondroitin sulfate PO q 24–48 hrs. See product label for specific doses.</td>
<td>For example, 13–15 mg/kg chondroitin sulfate PO q 24–48 hrs. See product label for specific doses.</td>
<td>Proprietary nutraceuticals may have variable efficacy and active ingredients. Choose those from companies with a good reputation. Initial dosing should occur until a response is noticed. Maintenance dosing is about half of the initial dosing. This can be decreased even further to maintain symptom relief.</td>
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<tr>
<td>Polysulfated glycosaminoglycans (injectable: 100 mg/ml)</td>
<td>5 mg/kg IM weekly OR 1.1–4.8 mg/kg IM every 4 days for 6–8 treatments, then as needed</td>
<td>5 mg/kg IM weekly OR Dogs and cats: 1.1–4.8 mg/kg IM every 4 days for 6–8 treatments, then as needed</td>
<td>There are no known contraindications unless the patient has a hypersensitivity to the compounds.</td>
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Not all drugs / dosages are approved for use by the FDA in the species indicated in this table.