NEWER OPTIONS FOR CHRONIC PAIN MANAGEMENT

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Chronic pain management is one of the most important aspects of veterinary medicine today, especially in geriatric patients. And yet, it is one of the most under developed areas of many practices. As a consequence to injury or as a component of the aging process, chronic pain can be a major influence in our patient's quality of life. In larger dogs, unmanageable pain is often the final determinant in the timing of their euthanasia.

There are many medications that we are all familiar with that form a basis for pain management. We have been the beneficiaries of the development of many excellent NSAIDs like Rimadyl (carprofen), Etogesic (etodolac), Metacam (meloxicam), Deramaxx (deracoxib), Previcox (firocoxib), and Zubrin (tepoxalin). The chondroprotectants, including Adequan and Cosequin amongst others, have been problem free adjuncts that have been well received by our clients even though clinical studies validating their efficacy are still lacking.

A brief review of the anatomic and neurophysiologic aspects of pain process are necessary to form a basis for more advanced multimodal pain management. There are three basic structural components in the pain pathway: the peripheral pain receptors with cell bodies in the dorsal root ganglia that synapse with the second order neuron in the dorsal horn of the spinal cord, the second order projection neuron that synapse with the third order neuron in the thalamic area of the brain stem, and the third order neuron that carries the pain impulse to the higher brain structures.

There are both protective and debilitating aspects to pain. Physiologic pain tells the body when it is at risk for tissue damage from temperature extremes, chemical agents, and direct tissue injury. Clearly, physiologic pain is protective. Initially, acute posttraumatic pain may be protective in that it encourages the patient to guard an injured area until healing occurs. But the pain and sensory pathways are susceptible to a variety of influences that alter the sensitivity and the structure of these neurons. The stronger the painful stimulus and the longer it persists, the greater the likelihood that chronic pain will continue well beyond the normal healing period. Chronic pain can be a debilitating affliction, the presence of which our patients are poorly equipped to effectively communicate to either owner or veterinarian.

The nociceptors (pain receptors) associated with physiologic pain have much higher thresholds than the sensory nerves responsible for general tactile information. There are different nerve types associated with the sensory (A beta fibers) and nociceptive (A delta and C fibers) receptors but they all form synapses with neurons in the dorsal horn of the spinal cord.

The inflammatory mediators that accumulate at the site of tissue injury cause an amplification of the pain response at the site of injury. With the nerve threshold lowered, even a light touch can evoke a strong painful sensation. This peripheral sensitization, often referred to as primary hyperalgesia, can be limited by many drug classes including NSAIDs, opioids, local anesthetics, and alpha-2 agonists.

Uncontrolled stimulation of the dorsal horn neurons can alter the sensitivity and the structure of these neurons. The stimulus threshold of these neurons decreases not only for the neurons directly associated with the primary nociceptors of the traumatized tissue but also for neurons associated with the normal tissues surrounding the injured area. Secondary hyperalgesia is the term used to describe the exaggerated painful sensations arising from relatively innocuous stimulation of the pain receptors in the uninjured tissues surrounding the site of injury.

To add insult to injury, the sensory nerve fibers may undergo a structural reorganization at the dorsal horn level. This leads to painful sensations from such innocent contact as the touch of a feather or the light touch of a cloth all mediated through the sensory fibers. This component of pain is referred to as allodynia.

Collectively, secondary hyperalgesia and allodynia make up what is commonly called central sensitization or dorsal horn windup. The net effect is that innocent sensations are perceived as pain and what should be mildly painful sensations are perceived to be very painful. NMDA antagonists, NSAIDs, opioids, local anesthetics, tricyclic antidepressants, anticonvulsants (gabapentin), and alpha-2 agonists can all help control central sensitization.

The final step in the pain pathway involves the delivery of the pain impulse from the thalamic region to the cerebral cortex triggering the conscious perception of pain. Although anesthetic block this perception of pain, they do NOT prevent the peripheral and central sensitization process from occurring. Opioids and alpha-2 agonists help control pain perception. In addition, sedative/tranquilizers can help reduce the perception of pain and the stress response that can contribute to the sensitization process. Alone, sedative/tranquilizers are not an appropriate substitute for proper analgesics but they are valuable adjuncts when included in a multimodal analgesic program.

The more severe and complex the pain process, the more likely you are going to need medications targeting different elements in the pain pathway. Borrowing from the work done in human pain management, we have a vast array of effective and reasonably safe methods for managing more serious pain in dogs and cats. All therapeutic programs should be associated with careful patient monitoring to include physical examinations and appropriate laboratory monitoring tests.

Conservative estimates suggest that no less than 20% of the canine population suffers from OA. It is also suggested that 90% of cats over 12 years of age have evidence of degenerative joint disease. This is a large group of patients that not only deserve our assistance but they can serve as a significant source of income for the practice. We can first look at osteoarthritis (OA) as an example of chronic pain management, then apply the same principles to other pain related problems.

Appropriate weight control may be the single most important aspect of OA management. Proper weight control, in and of itself, can reduce the frequency of OA development in at-risk dogs from 83% to 50%, altogether sparing 40% of the patients that would have developed this debilitating disease. Weight reduction in overweight OA dogs and cats can dramatically improve their comfort level and often helps to reduce the amount of medication needed for pain control. Appropriate exercise also is an important aspect of OA management.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are the most common medication group prescribed for OA and chronic pain management. No single drug in this class has proven consistently superior in analgesic efficacy or with respect to the potential for adverse drug effects.

While COX-2 preferential NSAIDs (carprofen, meloxicam) and the coxib class NSAIDs (deracoxib, foricoxib) have become popular and are consistently regarded as "safer" drugs than less selective NSAIDs, COX-2 suppression has its downsides. By selectively sparing COX-1, there has been a reduction in the frequency of NSAID related GI problems but COX-2 inhibitors can adversely affect important protective renal compensatory mechanisms and they can delay GI healing. Additionally, there are concerns about COX-2 inhibitors delaying bone healing in fracture patients. Whether lipoxygenase inhibition (tepoxalin) will be a real additional benefit is not yet clear.

ALL NSAIDs have the potential to cause both benefit and harm. Only by therapeutic trials and careful patient monitoring can you determine which, if any, NSAID best fits a given patient. Initial treatment failure may be discouraging, but additional trials with other drugs in the group will often reveal significantly more patient benefit.

NSAIDs are active at the peripheral and central level. They are capable of reducing the peripheral inflammatory response and they help manage central sensitization at the dorsal horn level. They should be used with caution, if used at all, in patients with preexisting gastrointestinal, renal, and hepatic disease. Monitoring for adverse effects is an important aspect of any chronic medication program. Adverse effects include gastrointestinal, renal, hepatic, and keratoconjunctivitis sicca related concerns.

Treatment considerations include: whether or not an SID medication would improve client compliance (etodolac, deracoxib, tepoxalin, and carprofen), whether or not the availability of inexpensive generics would relieve the burden of medication expense (etodolac), and whether or not administration would be easier for the client with a chewable (carprofen, deracoxib) or a rapidly disintegrating medication (tepoxalin).

NSAIDs should be used with great caution in cats. Whenever possible other analgesics and pain relieving modalities should be explored before committing to long term NSAID use in cats. Currently, meloxicam presents as the most appropriate choice for long-term NSAID therapy in cats.

- One common long term meloxicam dosing recommendation is 0.1 mg/kg (0.05 mg/lb) SC, PO for 1 to 3 days, then 0.025 mg/kg PO SID every 48 to 72 hours. For accurate dosing use TB or insulin syringe minus needle (Lascelles VAA 2007).
- Other suggestions include:
    - 0.05 mg/kg SC, PO on the first day followed by 0.025 mg/kg every 24 hours or less (titrate to lowest effective dose (Robertson VCNA: SAP 2008)
    - 0.01-0.03 mg/kg once daily (Gunew, et al FMS 2008)

Canine NSAID dosing:

CARPROFEN 4 mg/kg initial dose PO, SC followed by 2 mg/kg PO , SC every 12 hours (or, less ideally, 4 mg/kg every 24 hours)

DERACOXIB 3 to 4 mg/kg PO every 24 hours for up to 7 days, then 1 to 2 mg/kg PO every 24 hours

ETODOLAC 10 to 15 mg/kg PO every 24 hours

FIROCOXIB 5mg/kg PO every 24 hours

MELOXICAM 0.1 to 0.2 mg/kg SC, PO initial dose followed by 0.05 to 0.10 mg/kg SC, PO every 24 hours

TEPOXALIN 20 mg/kg initial dose followed by 10 mg/kg PO every 24 hours

TRAMADOL

Tramadol is an excellent choice for canine patients inadequately controlled on NSAIDs alone and for those intolerant of NSAIDs. Tramadol and its M1 metabolite, O-desmethyltramadol, exert a multimodal effect involving opioid, adrenergic, and monoamine receptors. As such, tramadol has both peripheral and centrally mediated analgesic benefit. Available in generic form, tramadol is a relatively inexpensive medication free of significant side effects. While tramadol can be a useful analgesic for cats its bitter taste and tendency to cause dysphoria limits its use in that species.

Initial dosing usually starts at 1 to 2 mg/kg BID to TID for cats; 3 to 5 mg/kg TID to QID for dogs. The dose can be increased up to 10 mg/kg QID for more difficult to manage canine cases. At these higher doses some sedation may be evident and constipation may occur with long-term use.

Tramadol is available in 50 mg tablets. It is compatible with most medications with the ***exception*** of the monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants (MAOIs like selegiline, SSRIs like sertraline, TCAs like amitriptyline).

Tramadol may decrease seizure threshold. It should be used with caution, if at all, in patients with a history of seizure activity. Tramadol may potentiate the sedative influence of other medications. Excretion is by both the hepatic and renal routes; a dose reduction would be appropriate in patients with impaired renal or hepatic function.

AMANTADINE

Amantadine is an NMDA (N-methyl-D-aspartate) antagonist capable of playing a critical role in acute and chronic pain management. NMDA receptors play a key role in the dorsal horn windup phenomena so crucial to central sensitization. Ketamine is an important in-hospital NMDA antagonist, analgesic adjunct, but ketamine is clearly not suited to home use. Dextromethorphan is also an effective NMDA antagonist, but its poor bioavailability when administered orally, its short half-life, and its rapid clearance make it less well suited to home analgesic use. Amantadine is the best-suited oral NMDA antagonist available for dog and cat pain management today.

Amantadine was originally developed as an anti-viral medication and has been also used to treat Parkinson's disease. It is an attractive "third man in" for patients inadequately managed on NSAIDs and tramadol or it can be teamed with an opioid alone (tramadol or oral morphine) in NSAID intolerant patients.

Amantadine is dosed at 3 to 5 mg/kg every 24 hours PO for both cats and dogs. It is available in 100 mg capsules and in a 10 mg/ml liquid form. While amantadine is considered safe when used

for long-term daily therapy, it is often effective as a pulsed therapy, giving it 2 weeks on followed by 1 to 2 weeks off drug. This can reduce drug expense and relieve some of the client's medication burden.

Although this drug has some monoamine reuptake inhibitory effects, those effects are dopamine specific and of no real concern related to serotonin syndrome when combined with tramadol, MAOIs, SSRIs, and TCAs.

This drug is primarily excreted, unchanged, in the urine. The dose should be reduced, and patient monitored closely, if used in patients with renal impairment. As a once-daily medication available in generic form, amantadine is not a very expensive addition to the pain management strategy.

GABAPENTIN

Gabapentin was originally developed as an anticonvulsant drug but it too can be an effective component of chronic pain management. It has been shown to be particularly effective in neuropathic pain management (pain from direct nerve injury) and cancer related pain. Although its exact mechanism is unknown, it has been shown to block central sensitization.

Gabapentin is useful for both dogs and cats. It is generally free of adverse effects or adverse drug interactions although some patients will show a transient drowsiness usually limited to a few days duration. Dogs are dosed at 5 to 10 mg/kg BID to QID PO although doses as low as 2 mg/kg BID have been reported to be effective in some cases. Cats are dosed at 2 to 5 mg/kg BID PO . It is available in 100 mg, 300 mg, 400 mg, 600 mg and 800 mg sizes. Use of the 50 mg/ml liquid product is not recommended due to its xylitol content. Gabapentin is a moderately expensive medication depending on dose and frequency.

This drug is primarily excreted, unchanged, in the urine. The dose should be reduced, and patient monitored closely, when used for patients with renal impairment. Gabapentin may potentiate the sedative influence of other medications. Withdrawal of this drug should be done gradually to avoid rebound pain.

AMITRIPTYLINE

Amitriptyline, the tricyclic antidepressant, is another drug with centrally mediated analgesic potential. This drug inhibits monoamine reuptake and, possibly, has some opioid receptor activity or opioid receptor enhancement activity.

Dogs are dosed at 1 to 2 mg/kg PO SID to BID. Cats are dosed at 2.5 to 12.5 mg total dose SID per cat. It is available in 10, 25, 50, 75, 100, and 150 mg tablets.

Amitriptyline should not be used with other TCAs, SSRIs, MAOIs, or tramadol due to the risk of serotonin syndrome. Its use with amantadine is not considered to be a problem for the reason noted above. Amitriptyline does have anticholinergic properties that should be taken into account, particularly, when planning anesthetic events. Amitriptyline may potentiate the sedative influence of other medications. This drug is metabolized by the liver. Dose reductions would be appropriate in patients with hepatic impairment. In addition, the patient's cardiac status should be monitored.

OPIOIDS

Opioids delivered by the transdermal, transmucosal, and oral route are often considered in the later phases of difficult pain management cases. Mu agonists like morphine and fentanyl are associated with more adverse effects than the medications discussed above. These scheduled drugs also require significantly more record keeping. Sedation and constipation are the most common of these unwanted effects. Drug tolerance can also complicate long-term opioid therapy. NMDA antagonists like amantadine can help reduce opioid tolerance.

The first-pass effect typically removes 85 to 95% of opioids absorbed from the gastrointestinal tract. This explains why buprenorphine and butorphanol are such ineffective analgesics when swallowed. Opioids are not without their ability to provide some analgesia when administered orally however. Codeine and morphine are two of the most commonly used opioid analgesics felt to be of benefit when given orally.

Codeine is a cost-effective analgesic when purchased as a generic in combination with acetaminophen. The #4 apap/codeine tablets contain 300 mg acetaminophen and 60 mg of codeine, the highest codeine to acetaminophen ratio. Dogs are dosed, based upon the codeine content, at 1 to 2 mg/kg BID to TID PO. The acetaminophen would, of course, preclude feline use. At this codeine dose, the acetaminophen dose is 5 to 10 mg/kg BID to TID, a dose consistent with that drug's use in canines. There is concern, however, about long-term acetaminophen consequences in dogs due to the fact that canines are not as efficient at metabolizing acetaminophen as people are. This concern limits the duration of apap/codeine therapy.

Morphine is a more attractive long-term oral opioid with oral bioavailability of about 15%. Dogs are dosed at 0.5 to 2.0 mg/kg QID PO . Cats are cautiously dosed at 0.2 to 0.5 mg/kg TID to QID PO. Morphine is available in capsule, tablet, and liquid forms. The sustained release morphine products offer no real advantage over the non-sustained release form when given to dogs and cats.

Fentanyl patches are not a particularly attractive long-term opioid analgesic. **Their efficacy is quite variable with some studies suggesting that 1/3 of cats fail to absorb therapeutic**

fentanyl levels. The patch would need to be changed every 3 to 5 days. Some patients develop pronounced dermatitis at the patch site.

Transmucosal buprenorphine, unlike oral buprenorphine, is an extremely effective, albeit somewhat expensive long term opioid analgesic for cats. Sheila Robertson's work has clearly shown that transmucosal absorption is an efficient method of buprenorphine delivery with the same bioavailability as IM administration. The clients are instructed to "tuck the syringe inside the cheek pouch". A less challenging routine than attempting to have the cat swallow a liquid medication over a sustained period of time.

There have been persisting suggestions that buprenorphine can an effective analgesic when mixed with V.A.L. syrup, clavamox, or amoxicillin for postoperative use in cats. Although this might seem attractive on the surface, it is not an appropriate use of this opioid due to the first-pass effect.

Constipation from long-term opioid administration, should it occur, can usually be managed through diet modification and by acupuncture at the GV1 acupuncture point.

LIDODERM PATCH

Lidocaine patches (Lidodermò) are less well known option for pain management. Although there is no systemic uptake, lidocaine patches applied over areas of pain have been shown to be beneficial for human and, it appears, veterinary pain management. Unlike fentanyl patches, Lidodermò patches can, and should, be cut to proper size and shape. They may be placed adjacent to, but not directly over, incisions, over areas of spinal pain, painful joints, bone tumors in peripheral limbs, and fractured bones. Ongoing work at the University level suggests benefit even in large dogs with pelvic fractures.

While the lidocaine patch will transfer drug into the tissue for up to 60 hours[i]. The patch should be applied to a clipped area of healthy skin. Wipe the area gently with a slightly dampened sponge to remove the loose hair and scale. Let the area dry then apply the patch. Cover the area with a bandage to help maintain skin adhesion but also to make sure the patient does not ingest the patch.

Patch ingestion can lead to lidocaine toxicity (CNS stimulation and CV depression). If you cannot adequately limit the patient's access to the area, do NOT use a lidocaine patch. The patch can usually be left in place for many days without causing any skin irritation. Each patch costs about $6.00. They should be available with a prescription from your local pharmacy or many of the full service medical suppliers. See http://www.vasg.org/drugs_sources_%26_costs.htm for suggested suppliers.

CONSTANT RATE IV INFUSIONS

Constant rate infusions can be an extremely beneficial step in the chronic pain management strategy. Severe pain can respond well to a combination of ketamine, lidocaine, and morphine. This combination works mainly at the dorsal horn level to quiet the sensitization process described above.

For more information on MLK CRIs see: http://www.vasg.org/constant_rate_infusions.htm.

Cessation of long-term analgesic therapy should be done gradually whenever possible. Gradual drug withdrawal would be most important when using the opioids and gabapentin. This is not necessary with respect to the NSAIDs and amantadine therapy.

In summary, by coordinating compatible medications and treatment modalities, the various aspects of the pain pathway can be targeted for a total benefit unachievable by any one medication alone. Balanced analgesia allows for lowered doses of any one drug, potentially allowing a patient to remain on a medication it would otherwise have been intolerant of. Therapeutic trials are normally required to help fine-tune the medication combinations for the most cost-effective and efficacious long-term management strategy with minimal adverse drug effects.

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[i] Plasma concentrations of lidocaine in dogs following lidocaine patch application. Ko J, Weil A, Maxwell L, Kitao T, Haydon T. J Am Anim Hosp Assoc. 2007 Sep-Oct;43(5):280-3.