MANAGING DIFFICULT PAIN CASES: 
NEUROPATHIC PAIN AND WIND-UP PHENOMENON
Nancy Shaffran CVT, VTS (ECC)

Twenty years ago pain management was making its first entry into human pediatric medicine and was still virtually unheard of in veterinary medicine. Managing and preventing pain in companion animals has become a contemporary, rapidly changing topic. Evidence showing that unrelieved acute pain can cause potentially life-threatening physiologic effects has shifted the prioritization of pain management. The question is no longer, “Do animals feel pain?” Today, the question is, “How do we best manage our veterinary patients’ pain?” The ability to alleviate patient pain has advanced significantly during the past 20 years. The International Academy of Pain Management was formed to bring this issue to the forefront of veterinary medicine and insure that the field would continue to grow wherever animals are being treated. Plans are completed to offer credentialing in the field of pain management for veterinarians and veterinary technicians. The first examination was held in August 2009.

The options for analgesia are ever increasing as our understanding of pain physiology improves. Choosing the correct analgesic therapy requires an understanding of both the pharmacokinetics of a wide range of drugs as well as the levels or type of pain associated with various conditions. The basic principles of current pain management include pre-emptive (preventative) analgesia; multimodal (using different classes of drugs simultaneously to interrupt the pain pathway at various points) and appropriate follow up analgesia (post-op and take home). The four traditional categories of drugs, NSAIDS, local anesthetics, opioids and alpha 2 agonists are still used in various combinations to inhibit the nociceptive process at more than one site. More recently several classes of drugs have been added to the pain management regime as adjunctive therapy in non-responsive cases. This includes NMDA receptor antagonists, anticonvulsants and antidepressants. No doubt as we learn more about wind up phenomenon and the specific roles of various receptors pain management will continue to be refined to allow for strategies which prevent pain and maximize pain control while reducing unwanted side effects.

NEUROPATHIC PAIN

Pain has traditional been subdivided into acute and chronic where acute pain is described as a sharp stabbing sensation and chronic as dull persistent throbbing. It may be more appropriate to classify pain as inflammatory (with subsets of acute and chronic) or neuropathic (existing in the nerves irrespective of ongoing inflammation). Neuropathic pain can exist along with inflammatory pain or as a separate syndrome and is described as persistent burning, itching or tingling sensation with or without present cause. Treating neuropathic pain has allowed patients to return to a state of normal or near normal by ameliorating these signs. The most common neuropathic pain reliever used in veterinary medicine in Gabapentin (Neurontin®).

Gabapentin (anticonvulsant) plays a role in reducing neuropathic pain and central sensitization in chronic pain patients. Gabapentin is becoming increasingly popular in both human and veterinary medicine as the first choice in patients whose pain does not respond to conventional therapies especially where nerve involvement is presumed. The primary indication for using gabapentin as an analgesic is to treat neuropathic pain.
However, gabapentin has been effective in treating chronic pain which was not considered to be neuropathic pain in humans & other animals. This suggests that neuropathic pain may be a component of some chronic/complex pain cases. The indications for initiating gabapentin therapy include:

- Chronic degenerative conditions such as osteoarthritis and cancer
- Dermatologic conditions such as lick granuloma, chronic skin or ear infections
- Persistent biting, licking, chewing, scratching at body areas
- Resistance to being touched at unaffected body sites
- Limping or obvious signs of pain not associated with current inflammation

Typical starting dose is 5-10mg/kg BIB to TID PO. Patients should be reevaluated for response frequently and dose adjustments are usually made every 3-5 days. Sleepiness is the side effect most commonly reported at higher doses. Caution: Neurontin® elixir contains xylitol

WIND UP PHENOMENON

Wind-up phenomenon is a very important newly understood concept in pain management. The vast majority of patients experiencing acute pain can be managed with conventional analgesics such as NSAIDS, opioids and local anesthetics but patients whose pain is unmanaged or who present in preexisting pain states may require additional therapy. Many patients stop responding to common analgesic drugs due to spinal cord wind-up.

The central nervous system adapts adversely to repetitive pain impulses after prolonged stimulation of nociceptors. This can cause a profound effect the nervous system’s architecture thereby altering pain processing. When spinal neurons are subjected to repeat or high-intensity nociceptive impulses, they become progressively and increasingly excitable even after the stimulus is removed. This condition is known as central sensitization or wind-up phenomenon and leads to nonresponsive or chronic intractable pain. Wind-up is the culmination of two distinct phases of change in the nervous system. First, pain transmitting nerve fiber threshold is reset. This resetting results in hyperalgesia where less and less stimulation is required to initiate pain. In the second phase, nerve fibers that normally carry non painful information are recruited and become part of the pain transmission process. This phase is termed allodynia and results in normally harmless sensations being interpreted as pain. The presence of hyperalgesia and allodynia collectively is considered wind-up phenomenon. This is apparent, for example, in the dachshund with disk disease that cries out in pain when any part of its body is touched, or the cocker spaniel with a chronic ear infection that can no longer tolerate normal petting. This phenomenon highlights the need for preemptive analgesia to treat pain before it begins and at regular intervals post-operatively.

Treatment or prevention of Wind-up

Pre-emptive analgesics, prevention of spinal cord wind-up and administration of adequate analgesia early in the pain process are key in preventing long term chronic pain states. In cases where NSAIDs and Tramadol do not provide adequate relief, the addition of gabapentin and or amantadine has been quite effective in many patients. N-methyl-D-aspartate (NMDA) receptor antagonists such as constant rate infusion of ketamine or
oral administration of Amantadine can enhance analgesia by blocking sensitization of neurons in the spinal cord and are especially useful for managing patients who have experienced wind-up phenomenon.

**Constant Rate Infusion (CRI)**

Constant rate infusion has proved to be one of the most reliable ways to provide adequate pain management to prevent windup and should be initiated as soon as wind up is suspected or expected. Many analgesic drugs can be safely and efficaciously administered by constant rate infusion. The most commonly used are local anesthetic (lidocaine), opioids (morphine or fentanyl) and N-methyl-D-aspartate antagonists (ketamine). Regardless of the drug, a loading dose is typically given immediately prior to beginning a CRI. These drugs can be used as single agents or in combination with one another.

**Morphine:** The main advantage of giving morphine as a CRI is the avoidance of peaks and valleys typically seen with opioid bolus dosing. A lower dose of morphine can be used in a CRI than in bolus dosing which can reduce the unwanted side effects of morphine such as dysphoria or panting. The CRI dose for morphine is:

- **Dogs:** 0.2-0.5 mg/kg SLOW IV loading bolus followed by 0.1-0.3 mg/kg/hr CRI
- **Cats:** 0.05-0.1 mg/kg IV loading bolus followed by 0.025-0.2 mg/kg/hr CRI

**Fentanyl:** Fentanyl is a full opioid agonist with similar properties to morphine. The main advantage of fentanyl over morphine is a rapid onset of action and short half life which allows for rapid cessation of unwanted side effects. The major disadvantage is that fentanyl is more expensive. The CRI dose for fentanyl is:

- **Dog:** 2-5 ug/kg IV loading dose followed by 5-20 ug/kg/hr CRI intraoperatively;
- **Cats:** 1-2 ug/kg IV loading dose followed by 5-20 ug/kg/hr CRI

**Lidocaine:** Lidocaine provides excellent systemic analgesia when delivered intravenously. Because it is safe for use in patients with GI disturbances lidocaine is a good choice for analgesia in patients with gastric dilatation volvulus (GDV) or other similar disorders. Lidocaine seems to also provide benefit for patients undergoing procedures with excessive nerve trauma such as complicated back surgeries or limb amputations. IV lidocaine is extremely short acting and can be discontinued without residual effect almost immediately. Lidocaine CRI should be discontinued if the patient shows signs of toxicity including muscle tremors, seizures, nausea or vomiting. The CRI dose for lidocaine is:

- **Dog:** 1-2 mg/kg IV followed by 30-50 ug/kg/min.
- **Cats:** There are reported lidocaine CRI dosages for cats but typically lidocaine is not recommended for use in cats due to potential for severe cardiotoxic effects.

**Ketamine:** Ketamine is a dissociative anesthetic and an N-methyl-D-aspartate (NMDA) antagonist. As an NMDA receptor antagonist, ketamine given as an intraoperative CRI binds at these CNS receptors and prevents “wind up”. Because of its mechanism of action, ketamine is best used to manage neuropathic types of pain particularly when the pain has been long standing and the patient has not responded well
to other analgesics. Ketamine should always be given in combination with an opioid and both can be delivered in the same infusion. The CRI dosage for ketamine is:
Dog and cat: 0.5 mg/kg IV loading bolus followed by 10 ug/kg/min CRI during surgery and 2 ug/kg/min for 24 hrs following surgery.

**Dexmedetomidine:** In 2008 dexmedetomidine (Dexdomitor) was introduced in the US and is rapidly replacing Domitor. Dexdomitor is the first premedication labeled for use in dogs and the first sedative labeled for use in cats. Most recently Domitor (and Dexdomitor) has been extensively used and valued as a 'rescue' drug for patients that are experiencing bad recoveries following anesthesia. Excitement in recovery (sometimes called 'emergence delirium') is not appropriate whether it is caused by pain or by residual effects of anesthesia. Excitement and pain both cause tremendous physiological stress and side effects that include tachycardia (high heart rate), hypertension (high blood pressure), cardiac arrhythmias (abnormal electrical activity of the heart), ventilation abnormalities (e.g., increased respiratory rate [i.e., tachypnea] with decreased volume of breaths [i.e., tidal volume]), cortisol release (which impairs proper healing) and a predisposition for gastrointestinal (GI) ileus and ulceration. This level of stress can cause severe problems in patients with cardiovascular or respiratory compromise. Domitor is an excellent choice (in heart-healthy patients) for treatment since it provides both sedation and analgesia. Patients who require repeated rescue doses of rescue Domitor can be placed on a low dose constant rate infusion (CRI) for continued sedation and analgesia. CRIs of dexmedetomidine are commonly used in human patients including children who are agitated in hospital, resistant to ventilators or in narcotic withdrawal. Similar success is reported in veterinary patients particularly in anxious breeds.

CRI dose for continued dysphoria/anxiety/pain in dogs and cats is 2ug/kg/hr. Can be added to other infusions