Innovations in Analgesia

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Pain assessment

"If you cannot measure it you cannot improve it" Lord Kelvin

Despite significant advances in pain management for companion animals, pain is still undertreated. One of the main reasons for this is the difficulty in recognizing and “measuring” pain in our patients, who cannot self-report. To treat pain, we must first look for it, recognize it and quantify it in some way so we can assess the efficacy of our interventions. Pain is a complex multidimensional experience with both sensory and psychological components. The sensory-discriminative component is “how it feels” (type, source and intensity of pain) and the affective-emotional component is “how does it make the animal feel?”

In humans who can self-report, pain is what the patient says it is but in neonates, cognitively impaired people and animals pain is what the observer says it is. As animal caregivers, we make “proxy” assessments on the patient’s behalf and this puts an extra burden on us, to “get it right”.

Acute pain assessment

Many attempts have been made to correlate objective measurements such as heart rate and blood pressure with pain. In cats, no study found a consistently reliable objective measure, which is not surprising since these parameters can be affected by many factors other than pain. Mechanical nociceptive threshold testing has proved a useful technique for evaluating both primary (wound) and secondary (remote areas unrelated to the wound) hyperalgesia in dogs and cats suggesting that an assessment of wound tenderness should be incorporated into an overall assessment of post-operative pain.

A painful animal may remain very still and quiet because they are painful and without interaction these animal will be overlooked.

Any system that is used must be valid, reliable, sensitive and not overly time consuming. Basic pain scales include simple descriptive scales (SDS), numerical rating scales (NRS) and visual analogue scales (VAS); these are considered unidimensional scales and do not capture all the complex emotions of pain.

It is now accepted that quantitative measurements of behavior are the most reliable methods for assessing pain in animals. Multidimensional systems are particularly important when self-reporting is not possible. However, they must incorporate components that have been proven as sensitive and specific indicators of pain in the species being studied. Knowledge of the normal behavior for the individual being evaluated is important and deviations from normal behavior may suggest pain, anxiety or fear, or some combination of stressors. Another area of research is the interpretation of facial expressions as indicators of pain. “Pain face” or grimace scales have been developed for rodents, pigs, cattle, horses and rabbits and preliminary work has been done with cats.

Acute pain assessment tools for dogs

The Glasgow Composite Measures Pain Scale is a validated tool for use in dogs and the short-form version is user-friendly and can be downloaded in several different languages at: www.newmetrica.com. The categories for assessment include: vocalization, attention to the wound or painful area, posture and movement, response to palpation and overall demeanor. Behaviors within each category or domain are assigned a number. If all categories are completed the maximum number is 24. In some patients (e.g. spinal cord injury) assessing
mobility is not possible but the other domains in this scale are still valid for those cases; without this category the maximum score is 20. This tool suggests an intervention score of ≥ 6/24 or ≥ 5/20. Other tools include the University of Melbourne Pain Scale which includes physiologic variables such as heart rate and blood pressure. [6]

**Acute pain assessment tools for cats**

We are also learning “what pain looks like” in our feline patients and two clinically useful tools are available. Brondani and colleagues have developed a multidimensional composite scale for use in cats based on behaviors and physiologic measurements following ovariohysterectomy. [7]

This tool along with many videos of assessing pain in cats is available at: http://www.animalpain.com.br/en-us/.

Another pain scale is the Glasgow Composite Measure Pain Scale-Feline. [8] This instrument is designed for surgical, medical, inflammatory or traumatic pain. The assessment domains in cats include: vocalization, posture, attention to the wound, response to people, response to palpation of the wound and overall demeanor. A scale that combines behaviors and facial expressions in cats [9] has been published [10] and is available for download at: www.newmetrika.com.

**Chronic pain tools**

In many cases chronic pain goes untreated in dogs and cats because owners assume that many behavioral changes that are due to pain are a result of “just getting old”. There are several Clinical Metrology Instruments (CMIs) available for use in dogs with osteoarthritis such as the Canine Brief Inventory, the Helsinki Chronic Pain Index and the Liverpool Osteoarthritis in Dogs (LOAD). In cats there are fewer to choose from but the Feline Musculoskeletal Pain Index is user friendly and is regularly updated as it becomes more widely used and tested. [11]

These tools involve cooperation between and input from both the veterinarian and owner. (See resources).

**Innovations in the treatment of pain**

Acute and chronic pain afflicts a substantial number of humans and animals and current treatment options do not fully meet the needs of all patients. We now know that poorly managed acute pain can progress to long term or maladaptive pain, so addressing perioperative pain in a multimodal and robust manner is essential. The most common cause of long term pain in dogs and cats is degenerative joint disease; this disease is not currently curable therefore treatment is aimed at managing the pain associated with it. Although non-steroidal anti-inflammatory agents are widely used they are not always fully effective or are associated with adverse side effects. An active ongoing goal of pain research is to better understand the underlying mechanisms of pain and to identify new specific therapeutic targets which should be more effective and have fewer unwanted side effects.

**Acute pain**

Acute must be treated until inflammation is minimal and unable to reinitiate the “pain pathway”. Although post-operative pain can last several days not all dogs and cats are sent home with analgesics even after routine neutering procedures; this is especially true of cats. [12, 13]

Whenever possible a local anesthetic should be incorporated into every surgery; they are the only class of drugs that can produce complete analgesia. One novel way to extend their efficacy is to use long acting formulations. A liposome formulation of bupivacaine that produces local post-operative analgesia directly at the surgical site has been approved by the FDA for use in dogs (Nocita®, Aratana Therapeutics). Currently it is labelled for cruciate surgery in dogs and is administered as a single treatment into the tissue layers during surgical closure and is released over time at the surgical site, providing local post-operative relief for up to 72 hours. Although off label it is being used for procedures such as amputations and mastectomies.
Preventing central sensitization

Preventing central sensitization or “wind-up” is a goal of perioperative analgesic protocols. This process occurs at the N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord. Ketamine has traditionally been considered as a dissociative anesthetic but its role as an analgesic and anti-hyperalgesic agent has evolved over the years in both human and veterinary medicine. Ketamine is a non-competitive NMDA receptor antagonist and therefore can modulate central sensitization and exert an anti-hyperalgesic effect. Given at low doses and as a constant rate infusion it had beneficial effects for major surgery including limb amputation and mastectomies. Ketamine also has anti-proinflammatory actions, which may provide additional benefits. In a clinical study dogs diagnosed with pyometra and undergoing surgery were sequentially allocated to receive a standard anesthetic and analgesic protocol, with or without low-dose ketamine infusion (not blinded). Serum C-reactive protein (CRP) was measured before, 24 and 48 hours after surgery. Low dose ketamine attenuated the post-operative increase of serum CRP.

Targeting novel mediators of pain

**Piprants** are prostaglandin receptor antagonists, a new class of selective compounds. What differentiates them from NSAIDs is that they act further down the inflammatory cascade by selectively antagonizing the prostaglandin E2 EP4 receptor; thus, maintaining normal activity of COX enzymes. The EP4 receptor has been identified as the primary receptor involved with the pain and inflammation of osteoarthritis. Grapiprant is a therapeutic agent in this class and has undergone development for use in dogs and cats. Safety and efficacy data are available and it has received FDA approval for use in dogs (Galliprant®, Elanco). This drug was safe and effective when administered long-term in the target population (2 mg/kg PO every 24h, for 28 days). Although not yet approved for use in cats information on its use has been published. Grapiprant is a therapeutic agent in this class and has undergone development for use in dogs and cats. Safety and efficacy data are available and it has received FDA approval for use in dogs (Galliprant®, Elanco). This drug was safe and effective when administered long-term in the target population (2 mg/kg PO every 24h, for 28 days). Although not yet approved for use in cats information on its use has been published.

**Nerve growth factor (NGF)** has been identified as an important mediator of inflammatory and neuropathic pain and is therefore a potential therapeutic target. NGF levels are increased in many naturally occurring acute and chronic pain conditions and in animal models of pain. Inhibiting or sequestering NGF alleviates hyperalgesia in many of these models. Current areas of study for targeting NGF include monoclonal antibodies to NGF or its tyrosine kinase receptor and sequestration of NGF with a soluble receptor protein with high binding affinity. Tanezumab, a human monoclonal antibody directed against NGF and administered by the intravenous or subcutaneous route has undergone human trials for a wide range of painful conditions including osteoarthritis, diabetic neuropathy, post-herpetic neuralgia and interstitial cystitis with good results although the benefit to risk ratio and optimal dose is still being defined.

In dogs, a fully caninised anti-NGF monoclonal antibody (NV-01, Ranevetmb, Nexvet Biopharma) has been developed; treatment must be species specific to avoid an immune response. In a preclinical trial using a kaolin model of inflammatory pain NV-01 reduced the signs of lameness, had a serum half-life of 9 days and was well tolerated. The target population for this drug are dogs with osteoarthritis. In one clinical trial, Canine Brief Pain Inventory scores decreased in dogs for up to four weeks following intravenous administration of NV-01. A felinized product has also been developed and early reports indicate adequate safety and efficacy for up to 6 weeks after a single SC injection (NV-02, Frunevetmb, Nexvet Biopharma) in cats with naturally-occurring degenerative joint disease.

**Neurokinin-1 antagonists**

Maropitant is a NK-1 receptor antagonist and inhibits binding of substance P to NK-1 receptors and is marketed as an antiemetic for dogs and cats. Maropitant is effective against a wide range of peripheral and central emetic stimuli. Because substance P is involved in pain pathways
Maropitant may have some analgesic properties. Preliminary work evaluating its anesthetic sparing effects suggests it may provide visceral analgesia in dogs and cats, but more studies are needed to define its role in pain management. \[24\]

**Selective neurotoxins**

Inhibition or destruction of specific nociceptive neurones without altering other sensory or motor functions is an attractive option for the control of severe pain. The vanilloid receptor which is present in the nociceptive neurones of the dorsal root and trigeminal ganglia has been targeted by resiniferatoxin (RTX) administered intrathecally in dogs with painful and debilitating bone cancers and osteoarthritis. \[25\] In dogs with bone cancer pain, relief was excellent. Substance P-saporin (SP-SAP) is a chemical conjugate of Substance P and a recombinant version of a ribosome inactivating protein (saporin). It acts as a targeted neurotoxin and selectively destroys cells in the dorsal horn of the spinal cord that bear NK-1 receptors. SP-SAP is given by intrathecal injection and has been studied in dogs. \[26\] In a prospective blinded controlled study of dogs with naturally occurring bone cancer, results during the first two weeks after treatment were equivocal but after two weeks the dogs that received SP-SAP had lower pain scores compared to dogs that received “standard of care” analgesic therapies (non-steroidal anti-inflammatory agents, tramadol and gabapentin), but some dogs in the SP-SAP group developed ataxia.

**Cannabinoids**

There is great interest in the use of “medical marijuana” by owners and veterinarians alike. All animals except insects have an endocannabinoid system. Hemp oil extracts and medical marijuana are possibilities for our patients but there can be toxicity problems. There is potential for use in pets with osteoarthritis and cancer pain if the correct receptors are targeted. Hemp oil tends to target the cannabidiol (CBD) and cannabinol (CBN) receptors and not the tetrahydrocannabinol (THC). Dogs are very susceptible to THC which is why true marijuana is potentially toxic in dogs. Currently any research on these compounds is hampered by the strict control of the product (DEA Schedule 1).

**References**

Resources and recommended reading

- Chronic pain tools – dogs
- Chronic pain tools – cats
  Feline Musculoskeletal Pain Index available at: https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/