The future of pain management in companion animals

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We are in exciting times with respect to pain control in companion animals. There is a lot of work going on to develop improved and novel therapeutics. Additionally, this work is creating more knowledge about how to measure pain, which, in turn, is allowing us to better understand what therapies are effective in controlling pain. This lecture will focus on giving delegates an overview of 3 new drugs that are approved and available in some parts of the world, or in the late stages of development.

These notes will focus on the monoclonal antibodies, but readers are also referred to information on the Piprants (https://www.ncbi.nlm.nih.gov/pubmed/27075237) and also on long-acting (72 hour duration) local anesthetics (http://onlinelibrary.wiley.com/doi/10.1002/vms3.43/full).

Degenerative joint disease and current treatments in dogs and cats

Despite some data to indicate efficacy of other drugs for OA-associated pain in dogs (1), evidence-based data indicates NSAIDs are currently considered the most effective therapy for DJD-associated pain (2), (3), (4). However, NSAIDs are not always sufficiently effective in dogs (1) and concerns about side effects result in a large unmet need in the treatment of canine DJD-associated pain. In cats there are greater concerns about the use of NSAIDs for long periods of time, especially as the majority of cats presenting with DJD-associated pain have evidence of chronic kidney disease (5).

A novel approach: Targeting nerve growth factor (NGF)

Targeting nerve growth factor (NGF) has emerged as a potentially useful therapeutic avenue for pain control. NGF was originally identified as a critical factor for the development and maintenance of sensory and sympathetic neurons in the developing nervous system. However, it is now clear that NGF has an important role in pro-nociception (reviewed in: (6)). Inhibition of NGF function via anti-NGF antibodies markedly reduces hyperalgesia and behavioral indicators of pain in various animal models of inflammatory arthritis. In human clinical studies, several anti-NGF mAbs have been evaluated and been shown to reduce pain and improve function in patients with OA ((7-9)).
The future: developing biologics for chronic pain control in cats and dogs

Antibodies need to be species-specific, or they will incite an immune reaction. Nexvet have developed an efficient way of creating species-specific antibodies, a process they term PETization (http://www.nexvet.com/our-science/petization-platform/). Using this approach, a canine-specific mAb against NGF (termed NV-01/ ranevetmab) was described and reported to have high affinity and potency, no effector activity, a long half-life and low immunogenic potential (10). The first exploratory clinical report suggested that this caninised anti-NGF mAb (200 mcg/kg IV) may provide alleviation of the signs of pain in dogs with osteoarthritis (11). Subsequent to this study, using a randomized, parallel group, stratified, double masked, placebo controlled, proof of principle clinical pilot study design, investigators assessed the pain-alleviating and activity enhancing effects of NV-01 in dogs with DJD-associated pain, using the primary outcome measures of clinical metrology instruments and actimetry (activity monitoring) data (12). There were significant differences between the groups favoring the anti-NGF antibody. No side effects were noted and neutralizing anti-NV-01 antibody responses were not detected. The magnitude of the effect appeared identical to that expected with an NSAID. These pilot study results were confirmed in a recently concluded large pivotal study (http://ir.nexvet.com/phoenix.zhtml?c=253841&p=irol-newsArticle&ID=2112528). Subsequent to these successes, a felinized version of an anti-NGF antibody was created (termed NV-02), and found to be safe in pre-clinical testing. Then, in a placebo-controlled, pilot, masked clinical study, thirty-four client-owned cats with DJD-associated pain and mobility impairment cats were randomized to a single treatment with NV-02 (n=23) or placebo (saline, SC [n=11]). The results demonstrated a 6-week duration of a positive analgesic effect, following a single injection, of this fully felinized anti-NGF antibody in cats suffering from DJD-associated pain (13). Larger studies are currently underway.

The development of efficacious anti-NGF monoclonal antibodies that are species-specific with low immunogenic potential and good safety profile heralds an exciting new era in pain management in dogs and cats.

References


Central sensitization in chronic pain: What is it and what does it mean?

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OA pain is classically considered as a nociceptive pain/inflammatory condition. In contrast to all the research and information known about cutaneous nociception, the nociceptive system of the joint has been less extensively investigated [6]. However, what is known is that local inflammation is an important part of the pathophysiology of the generation and maintenance of joint pain, with multiple mediators and systems involved, including prostanoids, free radicals, and nitric oxide. The mechanisms involved in local inflammation have been expanded recently with the recognition of the involvement of Toll-like receptors in the process [12].

The role of non-inflammatory processes is also becoming apparent, with a good example being nerve growth factor (NGF) [4]. NGF sensitizes and changes the phenotype of C fibers, with an important role in joint pain, that is currently the target of new biological therapies. Anti-NGF agents have already demonstrated important analgesic effects in OA pain, that might dramatically change analgesic strategies for OA pain. Another important component of OA pain is mechanical pain. In a normal joint, intraarticular pressure is between 2 and 10 mm Hg. In the presence of inflammation or local articular lesion, the pressure can rise to 20 mm Hg; and cartilage damage may induce increased pressure of the subchondral bone. Joints contain specific nociceptors that are specifically activated by mechanical stimuli.

As yet, it is unclear which components of the joint are most important with respect to the generation of nociceptive signals (pain).

However, the notion that OA is purely a peripheral problem has been challenged with the recent findings demonstrating the important role of central mechanisms in OA pain. In OA, as in all pain conditions, there is increasing evidence that central mechanisms and sensitization play an important role [6]. The pain transmission system is not hard-wired and set, but rather it is plastic - it alters in response to input. In general, the alterations that occur make the system more sensitive, and can create mechanisms that self-generate pain. The impact of non-peripheral joint mechanisms is clear when considering persistent chronic pain after total joint replacement [11]. Central sensitization manifests as pain hypersensitivity, particularly hyperalgesia (increased pain from a stimulus that would normally be painful at the affected joint and in areas of surrounding uninjured
tissue) and allodynia (pain resulting from stimuli that would not normally be painful such as touch). Altered activity in descending inhibitory pathways contributes to chronic pain; modulation of ongoing activity in descending pathways in chronic pain states can be detected by a change in conditioned pain modulation (or diffuse noxious inhibitory control) - the stimulus evoked inhibition of pain.

Central sensitization in OA has been confirmed by quantitative sensory testing (QST) analyses and functional MRI. [1-3,5,7-9] However, importantly, it is not known from this work whether the sensitization is driven by spinal cord changes, or alterations in endogenous descending pathways as have been described in humans [13], or, indeed, driven from peripheral mechanisms such as circulating sensitizing agents. The facilitated nociceptive transmission could be a product of all three mechanisms.

In terms of mechanisms driving central sensitization, little work has been done in OA, but glia (microglia, astrocytes) in the spinal cord have been found to be important contributors to facilitated pain states, including central sensitization [10]. Other findings have demonstrated the involvement of different brain regions. Spontaneous and continuous pain have been related to alterations in medial prefrontal and limbic cortical areas, regions that are involved in emotional state. Sleep, anxiety, depression and other affective states can all affect the OA-pain state [6].

Increasingly, it is being recognized that OA pain results from multiple processes throughout the body, and intense research is being undertaken to define the mechanisms and contributions of the different systems involved to an individual human’s pain state. What is clear is that one of the reasons for the difficulty in controlling pain in dogs may be the presence of central plasticity, as in humans with OA [1, 3, 8]. As such, central sensitization needs to be understood and treated appropriately.


Although many aspects of this spontaneous canine OA model have been well developed including: objective measures of limb use [11], objective measures of activity [17], validated owner-completed clinical metrology instruments [5,16], and measures of sleep disturbance [13], measures of enhanced processing of nociceptive stimuli resulting from peripheral and central mechanisms associated with spontaneous canine OA have received little attention until recently. Recently, QST measures have been explored in dogs as a measure of central sensitization.


Recognizing and treating feline chronic pain: osteoarthritis

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Degenerative joint disease (DJD) may be the most common disease of cats, and is a major cause of pain, decreased mobility, and decreased activity, (1) as well as changes in mood and social relationships with owners and caretakers (2) that may impact the human-animal bond. Recent studies have indicated the prevalence of radiographic DJD to be up to 92% in a randomly selected population of cats. (3) Unpublished data from our laboratory indicates that approximately 45% of cats with radiographic DJD show clinically detectable pain associated with this DJD. The diagnosis of DJD-associated pain is extremely difficult, currently relying on a combination of owner-noted changes in mobility and activity, and finding pain on manipulation of joints during veterinary orthopedic examinations. (1) These assessments are highly subjective, and radiographic findings do not correlate with orthopedic exam findings. (4) This may not be surprising given that radiographic and histological findings do not correlate well, (5, 6) and together, these data indicate that radiographic evidence alone is not a good indicator of DJD-associated pain. Clinical investigation of the efficacy of therapies for DJD-associated pain in cats currently relies upon owner-rating scales, which can be subject to a profound placebo effect. (7-9)

A recent report suggests that the overlap of DJD and chronic kidney disease (CKD) is higher than would be expected for either disease alone, with 68% of the cats with DJD in the study population also having CKD. (10) This underscores the need to not only assess cats for DJD, but also for CKD if therapies such as the NSAIDs are being considered.

The following information outlines how to approach diagnosing DJD-associated pain the feline patient. The description follows the clinical approach to a patient - gathering history; performance tests; orthopedic examination; radiography and other diagnostic tests. Other information on diagnosing chronic pain in cats can be found at: https://www.researchgate.net/publication/41656045_LONG-TERM_PAIN_IN_CATS_How_much_do_we_know_about_this_important_welfare_issue

History of impaired mobility & activity: In order to guide owners in their assessments of their cat’s mobility, we need to know what activities are altered by DJD-associated pain. Our group has also developed an owner-administered questionnaire for the assessment of feline musculoskeletal pain. {Benito, 2013 #5463;Benito, 2012 #13299;Benito, 2013 #12495;Gruen, 2014 #5570;Zamprogno, 2010
The instrument is available from: http://www.cvm.ncsu.edu/docs/cprl/cmi.html. This instrument is given to owners to complete, and the score can be used to assess the degree of DJD-associated pain and mobility impairment, and also to assess the efficacy of treatments.

**Performance tests**: DJD-associated pain results in impaired mobility. This can be evaluated through performance tests. This is difficult to do in the clinic with untrained cats, but some simple tests are:

- Place the cat down and allow it to move across the room - evaluate the fluidity of movement of the cat
- Encourage jumping off a chair or table
- Encourage jumping up to get into a carrier

For example, a cat with painful elbows may be very reluctant to jump down, resisting all attempts to encourage this. Cats with painful DJD loose the fluidity of movement that is so characteristic of normal cats. *This will be illustrated with video examples in the presentation.*

**Orthopedic examination**: Guidelines on how to perform a productive orthopedic examination in the dog are scarce, and virtually non-existent for the cat. Videos illustrating the approach are starting to be available: https://www.youtube.com/watch?v=rm7FSPG7pmo A few pointers are:

- Be prepared to spend some time on the examination
- Make the most of observations of the cat’s body balance including musculature and movement
- Have a calm but confident approach
- Have technical help that is calm, and confident with cats
- Handling cats should be performed with only the amount of restraint and that is necessary
- Use a room that is
  - Quiet
  - Away from dogs
  - Does not have ‘hiding places’ where a cat can get lodged in
- Use a surface that is soft and will not slip around (for example, a soft pad over a piece of thin yoga matting)
- Minimize restraint unless absolutely necessary
- Perform the examination in the position the cat is comfortable in (e.g. standing, lying, or in the owners arms)
- Be willing to ask the owner to leave while the examination is being performed. Depending on the owner, the cat may be more calm if the owner is not present
- Try to keep ones hands in contact with the cat continuously
- The examination should include every joint, and the whole axial skeleton
- In fractious cats, start with the areas suspected to be affected first
- Be willing to perform the examination in ‘stages’ – i.e., start, then come back to complete it later

**Drug treatments:**

There are concerns about the use of NSAIDs for long periods of time, especially as the majority of cats presenting with DJD-associated pain have evidence of chronic kidney disease (10). Because of these concerns, doses lower than the European-approved dose of meloxicam have been tried, and there are several suggestions from open label studies that these lower doses are effective in the management of feline DJD-associated pain. However, only one blinded, placebo-controlled study assessing a dose lower than the approved 0.05mg/kg daily has been performed, and that study found that 0.035mg/kg daily produced measureable improvement over a 3-week period of administration (7, 11). Indeed, only two placebo-controlled, masked, clinical studies of the efficacy of meloxicam in cats have been published (7, 11, 12). Robenacoxib is currently the author’s first choice NSAID in cats with DJD, despite the current lack of studies evaluating efficacy against placebo. In one efficacy and safety study, 155 cats with musculoskeletal pain were randomly allocated to one of three treatment groups - robenacoxib at 1.0-2.4mg/kg once daily, robenacoxib at 1.0-2.4 mg/kg twice daily, and ketoprofen at 1mg/kg once daily. The treatment duration was 5 or 6 days. There were no differences between the groups with respect to efficacy or tolerability over this short course. (13)

This encouraging safety profile is backed up by the 6 month safety study performed in support of the 3-day perioperative claim in cats in the US (http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM256758.pdf ). More recently, a large safety study evaluating robenacoxib in older cats with OA / DJD was published, and showed no safety concerns, even in cats with pre-existing chronic kidney disease (14).

Despite a complete lack of evidence of efficacy (the studies have not been performed) he author does use drugs such as gabapentin and amantadine, and suggested doses can be found at: https://www.researchgate.net/publication/41656046_DJD-Associated_Pain_in_Cats

Other new drug developments on the horizon will be discussed.

**Non-drug therapies:**

A particular diet and dietary composition has been shown to be effective for the partial allevation of chronic pain associated with degenerative joint disease in cats (9) The beneficial effects of this diet were probably due to the omega-3 fatty acid content, and the author recommends using a ‘joint support’ diet, or supplementing the diet with omega-3 fatty acids. Of interest is a supplement called PCSO-524, and recent experience in cats will be presented. PCSO-524 is available for humans (http://lyprinolusa.com) and also available for the veterinary market: http://www.antinolforpets.com). Various other non-drug therapies are useful in the management of feline OA pain, and these will be discussed.
References: