Nociceptive and neuropathic chronic pain: treatments for dogs and cats

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MATTHEW GURNEY looks at the management of chronic pain in pets, but says it is yet to be coupled to rigorous science to provide solutions in every case

CHRONIC pain can broadly be divided into two types – nociceptive (inflammatory) and neuropathic. A previous article (*VT* 43.17) focused on osteoarthritis, an inflammatory disease and the main cause of chronic pain in dogs and cats.

It is easy to appreciate inflammation is due to more than prostaglandins, which are the target of NSAIDs – our mainstay analgesic in osteoarthritis (OA).

Inflammation is just the start of the pain process. If inflammation is poorly controlled (we know very little about the ability of NSAIDs to deal with other inflammatory mediators – so NSAIDs understandably can't do the whole job alone), then peripheral sensitisation can occur. This may (but not always) lead to central sensitisation. A multimodal approach to therapy is therefore essential in dealing with central sensitisation, but good control hinges on the use of NSAIDs as the baseline. Of course, this may not be possible in every case, which is discussed later.

Assessment of chronic pain

Thorough assessment of chronic pain is difficult for the veterinarian in the time provided by a routine consult. These cases require time – so don't be afraid to book extra slots for these challenging cases.

The best person, in my opinion, to judge chronic pain is the owner. However, veterinary input is imperative as owners often require our direction to not only quantify that pain, but to evaluate it and its impact on their pet.

Fortunately, we have some tools to help us – termed client-specific outcome measures (CSOM) – used to assess chronic pain in dogs.

Of these, the most user friendly in my experience is the Canine Behavioural Pain Index (CBPI; Brown et al, 2008). This has been validated for use in dogs with OA and osseous neoplasia. It is composed of 10 questions examining the owner's assessment of pain and the impact the pain has on the dog's quality of life. This provides a useful baseline for you to determine the magnitude of the problem and an effective tool for the evaluation of treatment. The CBPI takes only five minutes for owners to fill in – I give it to them while they wait in reception. It can be downloaded from http://research.vet.upenn.edu/PennChart/AvailableTools/tabid/1969/Default.aspx

So far, there are no such tools for cats.

Owner education

Owner education can be a hurdle in chronic pain management. Most owners are very switched on and some suffer chronic pain themselves, so you can understand why they seek treatment for their pet. Regardless of the owner's own history, it is important to establish in his or her mind that the pet's problem is long-term and chronic pain management can be trial and error.

We do not have a long-term treatment for chronic pain that is as effective as the NSAIDs. Making this clear to the owner at the outset is really important. When a pet is started on an NSAID, most owners notice a vast improvement in the animal's comfort. If they expect that with adjunctive analgesics, they are likely to be disappointed. Disappointed owners either do not return to see you or will be resistant to further interventions.

Do not be afraid to be honest with owners. As negative as it may sound, we cannot provide an analgesic solution 100 per cent of the time to every single chronic pain patient. The reality is the pain may not get better.

Having said that, it is important to determine whether the lameness with which the dog or cat presents is due to pain or impaired function. Inability to use the limb or abnormal use of the limb is best addressed with physical therapy in conjunction with analgesics. Unwillingness to use the limb is most likely to be pain-related – an avoidance behaviour. I find it important to have this discussion with the owner because in many chronic pain cases you may not resolve a lameness with treatment: if the owner's sole focus is lameness resolution they will be disappointed and may discontinue treatment or seek advice elsewhere.

Diagnosis

This leads us nicely on to diagnosis. It is much easier to treat a condition if you understand the extent of the disease rather than hitting in the dark. The availability of advanced imaging techniques such as CT and MRI has enhanced our ability to effectively manage these difficult cases.

Table 1 shows the mainstays of treatment of OA. Many of these management points are equally appropriate to our patients suffering from chronic pain (many of which may have concurrent OA). Each of these components must be addressed, but it is often counterproductive to attempt to address all of these with the owner in one consultation. Book to see the owner for a follow-up consultation a week later – providing one week's worth of drugs and no more. Design a recording chart so owners can take away a copy of what you have discussed in the consultation, which you can use to record progression and document setbacks.

It is important owners recognise managing chronic pain is long term and the pet requires continuous medication rather than as required. The animal requires therapy and the owners require education.

The use of meloxicam at the lowest effective or reducing dose has been examined in arthritic dogs (Wernham et al, 2011). The authors reported: "Dose reduction is a less effective means of pain control compared with maintained dosing. However, NSAID dose reduction with maintained efficacy is possible, but success appears to be individual dog-dependent."

In practice, when I extrapolate this to other chronic pain aetiologies I find a benefit in continuous therapy. Primary pain in many chronic cases is nociceptive – due to the action of inflammatory mediators on nociceptors – and peripheral sensitisation may occur.

During inflammation, a high proportion of somatic peripheral nociceptors can be sensitised by various mediators, including bradykinin, prostaglandin, various leukotrienes, serotonin, histamine and, perhaps, free radicals.

Tissue injury activates C and A-? fibres to send action potentials to the CNS. If the injury is persistent, additional recruitment of A-? fibres and silent nociceptors occurs along with alterations in ion activity. The action potentials are propagated to the CNS and it is this kind of constant input that generates central sensitisation. Central sensitisation is defined as enhanced sensitivity of nociceptive spinal dorsal horn neurons to sensory stimulation.

Osteoarthritis is the number one cause of chronic pain in dogs and cats. Both peripheral and central sensitisation can occur in OA.

A neuropathic (NeP) component should be suspected in cases of chronic pain. Pain that is not well

controlled by conventional analgesics (opioids and NSAIDs) should raise the index of suspicion of NeP. This type of pain is often described as burning, shooting or stabbing by sufferers.

Features of NeP include:

• allodynia – a painful response to an innocuous stimulus, assessed by lightly stroking the skin;

• hyperalgesia – an increased response to a painful stimulus, assessed by the response to a pin prick;

• altered skin sensation; and

• dysaesthesia (an unpleasant abnormal sensation that can be spontaneous or evoked).

The pathophysiology of NeP is due to complex changes in the physiology of the nerve and not due to peripheral nociceptor stimulation (as in inflammatory pain).

Ninety per cent of NeP arises from the peripheral nervous system, although there is growing evidence many chronic pain conditions such as low back pain in man have a central neuropathic component. For a discussion of the mechanisms of NeP, the reader is referred to my previous article “So what is neuropathic pain?” (*VT* 43.17).

Drug therapy in chronic pain

NSAIDs are the mainstay of analgesic management in chronic pain. Their main points are as follows.

• NSAIDs are licensed.

• We are familiar with the efficacy and side effect profile of these drugs.

• No one NSAID is superior in dogs.

• Work suggests a benefit to robenacoxib over meloxicam in cats after surgery (Kamata et al, 2012).

• If one NSAID doesn’t seem efficacious, switch NSAIDs. If side effects are a concern, switch NSAIDs.

• If switching, use a washout period of five days – during which you can move to a second line drug. I always warn the owner second line drugs are unlikely to produce analgesia as good as NSAIDs.

• Consider compliance in NSAID dosing – a drug that is easy to give will win every time and there is now a variety of formulations available.

• Use of NSAIDs in cats is well summarised by the ISFM/ AAFP document on long-term NSAIDs in cats – essential reading (Sparkes et al, 2010).

• Any animal in pain should receive an NSAID unless a clear contraindication exists.

Remember to consider the context in which you are using NSAIDs. Yes, NSAIDs are contraindicated in renal and hepatic disease; however, if you are treating a pet with a terminal condition and NSAIDs are the best analgesics for the pet's pain and thus quality of life, then continue.

If pain control with NSAIDs is poor, the pet will not tolerate NSAIDs, or there is a contraindication, where should we look next?

Should our second line drug be a licensed drug (with limited evidence of efficacy) or an unlicensed drug, such as amantadine, which has documented efficacy in dogs with OA (Lascelles et al, 2008)?

I'm sure most vets reach for tramadol due to familiarity. There is now evidence tramadol is beneficial in terms of analgesia in dogs with OA (Malek et al, 2012); however, tramadol is not effective in every case.

In reality, any of these three drugs would be a good choice and I recommend the practitioner consults the *BSAVA Formulary* for dosing and user considerations.

Second line in cats

There are several factors to consider in cats with adjuvant analgesics. The efficacy of tramadol in cats has been found to be variable. If you prescribe tramadol for a cat, warn the owner of this variability and decide if it works for the individual.

Tramadol at 2mg/kg to 4mg/ kg per os demonstrates thermal antinociception in cats (Pypendop, Siao and Ilkiw, 2009) and 2mg/kg tramadol IM produced comparative analgesia to pethidine (Murison et al, 2010).

Gabapentin is used anecdotally in OA in cats. Its efficacy has been documented in trauma cases (Vettorato and Corletto, 2011). The pharmacokinetics of amantadine 4mg/kg per os have been studied in cats and demonstrate a plasma half-life of five hours (Siao et al, 2011b). These authors also studied the antinociceptive effect with the following conclusion: "Overall, amantadine did not reduce the antinociceptive dose of oxymorphone. However, an effect was likely produced in some cats. These results suggest that amantadine may be useful to reduce the analgesic dose of opioids

in cats in clinical practice, but that analgesic treatment will need to be tailored to the individual's response" (Siao et al, 2011a).

Two drugs or one?

Two drugs being better than one is the idea behind multimodal therapy. I always start with an NSAID plus second line drug. I judge efficacy on the owner's report with the CBPI to assist this. At this stage you may need to consider a third line drug or acupuncture.

My third line choice would be gabapentin. Although there is no documented efficacy of gabapentin in dogs beyond case reports for neuropathic pain, I see good results and few side effects. See my previous comment regarding cats.

It is easy to appreciate pharmacological intervention in such cases is often based on anecdote and experience, in the absence of solid science.

Case studies

Case study 1. An eight-yearold cocker spaniel presents with lumbar pain. MRI confirms disc protrusion and lumbar nerve root compression, which is not amenable to surgical treatment. The dog receives an NSAID, to which there is an initial improvement.

The type of pain experienced by the dog is likely to be neuropathic, but probably also inflammatory pain, due to the positive response to the NSAID (which I would continue).

Gabapentin 10mg/kg per os bid would be a logical choice, given its value in treating neuropathic pain in people and case studies documenting efficacy in dogs. Gabapentin is associated with few side effects in dogs (mainly sedation at higher doses) and is hepatically metabolised in dogs; therefore, with long-term use periodic (every six months) blood sampling is recommended.

Despite a lack of randomised controlled clinical trials in dogs, I have used gabapentin to good effect in similar cases. Likewise, my experience with acupuncture in these cases is positive.

Case study 2. A 10-year-old cat presents with unstable diabetes mellitus. On examination the clinician notes weakness in one pelvic limb with a plantigrade stance. This raises the suspicion of diabetic neuropathy, which is reported in cats. We know from our human colleagues that diabetics often describe pain, stiffness and unusual limb sensations with this condition.

In addition to insulin therapy the cat is started on gabapentin 50mg per os bid, to which it showed an improvement in pelvic limb function, and continues to do well three months later.

Case study 3. Your colleague consults you about a nineyear- old Rottweiler with radiographic

evidence of osteosarcoma in the proximal humerus. The dog suffers with bilateral elbow OA, for which it receives daily meloxicam. Until recently, this has kept the dog comfortable. Amputation is not an option as the dog is severely overweight.

Blood screen reveals elevations in urea and creatinine suggesting mild renal insufficiency. The owner has completed a CBPI, which suggests pain control is reasonable, but there is potential for improvement.

Very little information exists on management of pain due to osteosarcoma; however, in the author's experience, pain is moderate to severe and requires multimodal drug therapy.

Given the palliative nature of this case and the positive response to NSAIDs, despite the renal insufficiency, I advised the owner to continue NSAID therapy. This approach should be discussed with the owner, with quality of life being the paramount concern.

One study suggests in cats with chronic kidney disease of IRIS stage I or II, chronic long-term NSAID therapy did not influence the progression of renal disease, however no such studies are available in dogs. There is no evidence that COX-2 selective drugs are any safer than COX-2 preferential NSAIDs.

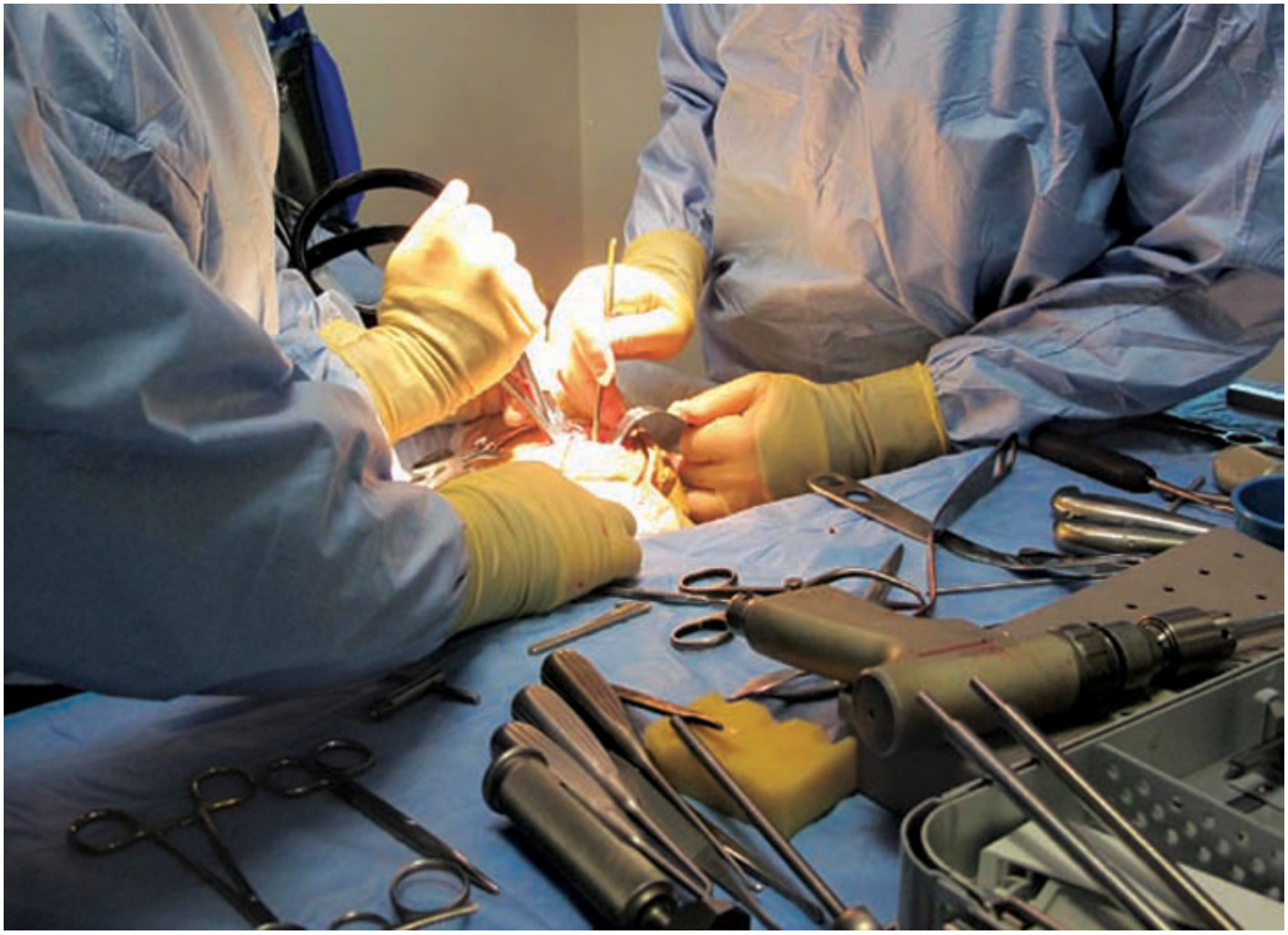
Given the exacerbation of the pain despite NSAID therapy, this dog would benefit from the addition of adjunct analgesics. Note that if pain is considered severe, hospitalisation and administration of injectable opioids may be the best course of action to treat the acute flare.

In osteosarcoma cases, I have used combinations of gabapentin and tramadol or gabapentin and amantadine to improve comfort. I always suggest acupuncture as an option. Physiotherapy and massage should be considered once the acute pain has improved and provided the pain is not made worse by intervention.

References

- Brown D C, Boston R C, Coyne J C et al (2008). Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis, *JAVMA* **233**(8): 1,278-1,283.
- Kamata M, King J, Seewald W, Sakakibara N et al (2012). Comparison of injectable robenacoxib versus meloxicam for peri-operative use in cats: Results of a randomised clinical trial, *Vet J* **193**(1): 114-118.
- Lascelles B D X, Gaynor J S, Smith E S, Roe S C et al (2008). Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs, *J Vet Int Med* **22**(1): 53-59 doi:10.1111/j.1939- 1676.2007.0014.x
- Malek S, Sample S J, Schwartz Z et al (2012). Effect of analgesic therapy on clinical outcome measures in a randomized controlled trial using client-owned dogs with hip osteoarthritis, *BMC Vet Res* **8**:185 doi:10.1186/1746-6148-8-185.

- Murison P J et al (2010). Use of tramadol in cats undergoing ovariohysterectomy, Association of Veterinary Anaesthetists spring meeting, Cambridge. Pypendop B H, Siao K T and Ilkiw J E (2009). Effects of tramadol hydrochloride on the thermal threshold in cats, *Amer J Vet Res* **70**(12): 1,465-1,470 doi:10.2460/ajvr.70.12.1465.
- Siao K T, Pypendop B H, Escobar A, Stanley S D and Ilkiw J E (2011a). Effect of amantadine on oxymorphone-induced thermal antinociception in cats, *J Vet Pharm and Ther* **35**(2): 169-174 doi:10.1111/j.1365-2885.2011.01305.x
- Siao K T, Pypendop B H, Stanley S D and Ilkiw J E (2011b). Pharmacokinetics of amantadine in cats, *J Vet Pharm and Ther* **34**(6): 599-604 doi:10.1111/j.1365-2885.2011.01278.x.
- Sparkes A H, Heiene R, Lascelles B D X, Malik R et al (2010). ISFM and AAFP consensus guidelines on long-term use of NSAIDs in cats, *J Fel Med and Surg* **12**(7): 521-538 doi:10.1016/j.jfms.2010.05.004.
- Vettorato E and Corletto F (2011). Gabapentin as part of multi-modal analgesia in two cats suffering multiple injuries, *Vet Anaesth Analg* **38**(5): 518-520 doi:10.1111/j.1467-2995.2011.00638.x.
- Wernham B G J, Trumpatori B, Hash J, Lipsett J et al (2011). Dose reduction of meloxicam in dogs with osteoarthritis-associated pain and impaired mobility, *J Vet Intern Med* **25**(6): 1,298-1,305 doi:10.1111/j.1939-1676.2011.00825.x.
  www.vetoquinolusa.com/Studies/CKD/StateOfTheArtProceedings.pdf



The link between surgery and chronic pain is of much debate.

Dosing NSAIDs – ensuring compliance is important.

TABLE 1. Management guides for pain of osteoarthritis can be effectively applied to most cases of chronic pain, regardless of aetiology
Management strategies
Analgesics
Weight management
Diet
Controlled exercise
Environment modification
Physical therapy
Acupuncture

TABLE 1. Management guides for pain of osteoarthritis can be effectively applied to most cases of chronic pain, regardless of eotiology