



Pain Management in Small Animals Mini Series

Session Three: Chronic Pain Management

Dr. Jo Murrell, BVSc. (hons), PhD, DipECVAA, MRCVS



What is chronic pain?

Within the veterinary profession there is widespread agreement that recognition of pain is a highly subjective and complex field that is continually evolving. Whilst most clinicians believe that their ability to identify and quantify acute pain in dogs is good, many would admit they lack the tools to accurately recognise and quantify chronic pain.

Indeed what is the definition of chronic pain? Previously, chronic pain was described as pain lasting more than 3 or 6 months, but now many clinicians are diagnosing chronic pain as pain that extends beyond the period of tissue healing. It should be emphasised that chronic pain doesn't have a purpose and offers the animal no advantage in terms of survival. Chronic pain is not just a prolonged extension of acute pain, it signals that wide ranging physiochemical changes have occurred in the central and peripheral nervous systems, from the level of the peripheral nociceptors, to the cerebral cortex, causing a persistent hypersensitivity to pain.

Identification and quantification of chronic pain

So chronic pain is a complex experience with emotional and cognitive components that can have a substantial impact on the patient's quality of life; but how does the veterinary surgeon, nurse or owner actually identify and measure the degree of pain in their patient or pet? When trying to recognise and quantify chronic pain it is important to remember that there are three different aspects that contribute and determine the experience of pain in animals, as in man. These are broadly classified as i) the intensity and location of pain (i.e. where does it hurt and how much does it hurt?) ii) the emotional component of pain, the element that causes the suffering associated with chronic pain and iii) the cognitive aspect of pain. It is difficult to conceptualize the cognitive aspect of pain in animals, but in humans it refers to the interaction between sensory and cognitive factors that determine the pain experience, for example distraction techniques to reduce pain severity.

Changes in activity and behaviour are most commonly used to identify chronic pain in dogs. A list of characteristics commonly associated with pain in dogs is shown in Table 1, but in actual fact any change in behaviour, or an absence of a behaviour may be suggestive of pain! It is important to consider the potential for pain in all dogs presented with chronic disease and evaluate these animals carefully in conjunction with the owner.

In order to incorporate the emotional and cognitive aspects of pain into quantification of chronic pain in dogs, recent assessment tools focus on measurement of quality of life (QoL). There has been most emphasis on the development of QoL instruments for quantification of pain associated with osteoarthritis, reflecting the prevalence of the condition in the dog population. However despite numerous attempts to develop, validate and utilise QoL questionnaires in dogs we still lack a 'gold standard' for criterion validity. At the end of these notes references to some of the questionnaires are provided, for both osteoarthritis and cancer pain in dogs. It can be useful to incorporate a QoL questionnaire into your clinical practice to facilitate management of chronic pain in dogs with different disease conditions.

Veterinary surgeons are well placed to assess the intensity and location of pain, but it is imperative to involve the owner in decision making about requirement for, and response to, pain management strategies, including drug therapy. Studies in dogs with osteoarthritis have shown that owners are very adept at quantifying pain in their own animals (Hielm-Bjorkman et al. 2003), and due to the close interaction between owners and dogs, they are best placed to evaluate the emotional impact of pain on their pet. However some owner education may be required. Although careful questioning usually prompts the owner to recall changes in the behaviour of their pet that are likely to be indicative of pain, in geriatric patients, these changes in behaviour are commonly wrongly interpreted as normal changes associated with aging. Many behavioural changes associated with pain and an accompanying decreased QoL are very subtle, such that it is important to emphasize the language

and words that are required to allow the owner to effectively communicate these changes to the veterinary surgeon.

Changes in activity are a useful outcome measure to evaluate the success of therapeutic interventions in dogs with osteoarthritis and Lascelles and colleagues (2008) recommend using Client Specific Outcome Measures (CSOM) as a sensitive tool to evaluate analgesia in dogs with osteoarthritis. CSOM require the owner to identify time and place specific behaviours (usually 4 or 5 of them) that they consider to be altered in their own pet and to grade the degree of impairment compared to a precise age when they considered their dog to be normal. For example the owner might identify that their dog no longer jumps on the bed at night. The owner is then required to rate the degree of impairment in this activity on a scale (for example, no problem, a little problematic, quite problematic, severely problematic, impossible). At follow up appointments the owner is asked to re-grade the degree of impairment in this activity (and the others) in order to evaluate the successfulness of the analgesic intervention and whether further strategies to improve pain management are required.

In referral centres objective measures of pain such as force plate and gait analysis may be used to quantify chronic pain associated with osteoarthritis. It is important to remember that changes in gait do not relate to the dog's own emotional and cognitive experience of pain but reflect pain intensity and location as well as mechanical dysfunction associated with osteoarthritis.

Table 1: Weblinks for three owner questionnaires that can be used to monitor pain in dogs with osteoarthritis.

Questionnaire	Web link to download the questionnaire
Canine Brief Pain Inventory	http://www.vet.upenn.edu/research/clinical-trials/vcic/pennchart/cbpi-tool
Helsinki Chronic Pain Index	http://www.vetmed.helsinki.fi/english/animalpain/hcpi/
Liverpool Osteoarthritis in Dogs	http://www.bristol.ac.uk/media-library/sites/vetscience/documents/5%20Liverpool%20Osteoarthritis%20in%20Dogs%20(LOAD).pdf

Possible signs of pain in dogs	
Postural	Abnormal posture, or lying in an abnormal position, inability to rest easily, hunched up position or guarding of the abdomen or another body part
Movement and gait	Inability to weight bear on a limb, lameness, inactivity or restlessness, weak tail wag, less inclined to jump up, increased daytime sleeping or decreased sleeping at night
Vocalisation	Some animals may be silent, others whine, scream, whimper, bark (more or less) growl, attempt to bite
Wound/pathology	Biting, chewing or licking painful area, inappropriate response to area being touched
Demeanour	'Depressed' look, little interaction, altered tail carriage, less grooming, less enthusiasm to exercise/go for a walk
Absence of normal behaviours	Failure to do normal things such as stretch out, less vigorous shaking etc, less playful/curious, appetite changes
Urination/defecation	Urinates/defecates without moving or in inappropriate places because the dog cannot move/get up
Other	Tachypnoea, panting, tachycardia, dilated pupils, increased blood pressure

Table 1. Physical characteristics of pain in dogs. Not all signs are indicative of pain in all patients, and some may be normal behaviours for individual dogs. Do not neglect "absence" of behaviours as an indicator of chronic pain.

Measuring pain in cats with osteoarthritis is challenging due to the subjective experiential nature of pain combined with the fact that chronic pain is likely to vary over time. Furthermore, chronic pain is likely to have a negative impact on quality of life in cats, a construct that is very difficult to measure unless the assessor is familiar with the animal and their day to day demeanor.

Until recently an owner questionnaire to quantify pain associated with osteoarthritis was lacking in cats; this has now been rectified by the development of the Feline Musculoskeletal Pain Index (FMPI) (Benito et al 2013 a,b). The index is freely downloadable from <http://www.cvm.ncsu.edu/docs/cprl/fmpi.html>.

The FMPI comprises 18 different questions relating to how mobile a cat is (walking, jumping up, jumping down, climbing stairs), and behaviours that may be more indicative of quality of life e.g. interaction with other cats and family members, play related behaviours, grooming. For each question there are seven different possible responses ranging from "above normal" to "not at all" or "doesn't apply or I don't know" and the owner has to tick the most appropriate response.

No numerical score is applied to any of the possible answers so that an owner's responses are not skewed by a value being assigned to any one possible response. One potential disadvantage of the index is that it relies on the owner being aware of what is "normal" for a cat, which may be difficult some owners and skew the results, although the authors of the index do not report it to be problematic.

There are also three additional questions that relate specifically to pain and quality of life:

- "check the square that best describes your cat's pain over the past week"
- "check the square that best describes your cat's pain today"
- "please rate your cat's overall quality of life (How well can he/she do his/her favourite activities, eat and move around?)"

Asking owners to directly consider their pet's quality of life can be very helpful in decision making about the optimal time to implement analgesic therapy, change analgesic therapy or even consider euthanasia.

In order to analyse a completed index the authors have (post completion) assigned scores to the different possible answers ranging from -1 (above normal) to 4 (not at all) for activity type questions. The pain and quality of life questions have four possible different answers ranging from 0 (no pain or excellent quality of life) to 4 (severe pain or poor quality of life). This gives a total possible score of 83 corresponding to maximum impairment or pain. To date, no intervention criterion where administration of analgesics is indicated has been determined.

The FMPI has been shown to discriminate between normal cats and cats with pain caused by osteoarthritis (Benito et al. 2013a) and also showed good test-retest reliability when owners were asked to complete the questionnaire twice two weeks apart (Benito et al. 2013a). However, somewhat surprisingly, the index did not perform well in a study designed to investigate the responsiveness of the index (i.e. whether the instrument could detect a change in osteoarthritis related pain because of treatment) (Benito et al. 2013b), suggesting that some further refinement of the scale is needed. However, it is currently the owner questionnaire available to assess chronic pain associated with osteoarthritis in cats and the author has found it helpful in decision making regarding pain management in cats with osteoarthritis.

When should pharmacotherapy for chronic pain be initiated?

Decision-making about whether or not to start dogs presenting with signs of chronic pain in the consulting room on pharmacotherapy can be challenging. Firstly, it is not uncommon for owners to be surprised when a discussion about whether their dog is painful is raised. This is particularly the case if the dog is presented for a routine vaccination or concurrent disease problem. Some owners can be resistant to the concept of drug therapy if its unexpected, particularly if they are not convinced that their pet is painful. Secondly, the only class of analgesic drug licensed for the management of chronic pain in dogs, non steroidal anti-inflammatory drugs (NSAIDs), have well recognised side effects that can have serious adverse consequences for the animal if they arise. Therefore careful decision-making is required about the benefits of drug therapy, particularly NSAIDs. However the negative welfare consequences of chronic pain and the impact that chronic pain has on the well being of an animal must always be considered. Every effort must be made to provide analgesia, either with NSAIDs, a different class of analgesic drug or using non-pharmacological therapies such as diet supplementation, disease modifying osteoarthritis drugs and weight reduction (if the chronic pain is caused by osteoarthritis), heat or cold therapy. Generally non-pharmacological therapies either take some time to become effective (e.g. weight loss, diet supplementation) or are too impractical to provide continuous analgesia when used alone (e.g. heat or cold therapy). Therefore in most dogs that present with signs consistent with chronic pain, immediate pharmacological therapy will be indicated for the provision of analgesia. However adjunctive medical strategies should not be ignored,

particularly for the management of pain associated with osteoarthritis. Consider starting the dog on analgesic therapy while talking to the owner about other non-pharmacological strategies that can be implemented concurrently, so that a holistic approach to the management of chronic pain is adopted. For example, modifications to the home environment are simple for owners to achieve, and for animals with mobility problems, have the potential to rapidly improve quality of life. Sawaya (2007) has written a review of physical therapies in the management of arthritic patients that serves as a good starting point for further reading about non-pharmacological therapy for osteoarthritis. When reading about alternative therapies it is important to concurrently evaluate the evidence base to support adoption of each treatment. Unfortunately in the veterinary literature there is a very limited evidence base to support any strategies to manage chronic pain (including, with the exception of NSAIDs, most analgesics), but some techniques are better recognised and have been more thoroughly evaluated than others.

Drug therapy for chronic pain in dogs

NSAIDs should be the first line treatment for chronic pain unless contra-indicated in an individual patient. There is a good evidence base to support the efficacy of NSAIDs in the management of chronic pain, plus there are a large amount of data to support the recommended dose and dosing interval for all licensed NSAIDs in dogs. The most significant potential side effects associated with the administration of NSAIDs for chronic pain are:

1. Gastro-intestinal effects including vomiting, diarrhoea and a degree of gastro-intestinal ulceration. Mild GI side effects occur relatively frequently in dogs starting NSAID therapy, and usually wane within the first 7-14 days of therapy. Severe GI side effects, such as ulceration and bleeding, or at worst GI perforation, are less common, but are also more likely to occur within the first two weeks of therapy. Clinical signs associated with GI ulceration and / or perforation include haematemesis, melena and persistent vomiting. The owner should be warned about the potential for GI side effects and advised when to stop NSAID administration and seek further advice from a veterinarian.
2. The major renal side effect of NSAID therapy is reduced renal blood flow during periods of hypotension that can result in renal ischaemia and persistent renal dysfunction. Hypotension is less likely to occur in animals prescribed NSAIDs for chronic pain compared to animals given NSAIDs around the time of anaesthesia and surgery, however may still develop if the dog becomes dehydrated through reduced water intake or excessive loss (e.g. due to persistent vomiting). Warn owners about the potential for dehydration during NSAID therapy to cause renal complications, so that veterinary treatment and intravenous fluid therapy can be initiated promptly for dogs when appropriate.
3. NSAIDs are known to cause an elevation in liver enzymes (for example ALT, ALKP), however overt liver dysfunction following administration is very uncommon in dogs and usually attributed to an idiosyncratic reaction, or abnormal metabolism of NSAIDs in individual animals.
4. Hypertension is not uncommon in humans taking NSAIDs, particularly COX-2 selective drugs. This is attributed to the renal effects of NSAIDs resulting in sodium and therefore water retention. The incidence of hypertension in dogs receiving NSAIDs has not been documented, but it is important to be aware of this side effect, particularly in animals with known cardiovascular disease.
5. NSAIDs are known to have effects on blood clotting, via either reduced production of thromboxane A₂ or prostacyclin depending on the COX 1: COX-2 selectivity of the individual NSAID. The most common effect is reduced blood clotting (manifest as a more prolonged bleeding time), although as long as the dog is not undergoing surgery this is rarely of clinical significance. In humans some COX-2 specific NSAIDs have the potential to cause an increased risk of thrombosis, although this risk has not been investigated or quantified in dogs.

How do these side effects modulate decision making about NSAID therapy?

Animals with chronic pain commonly have concurrent disease and / or are clinically geriatric, which may modify the pharmacokinetics of some NSAIDs. However, although no precise data on the incidence of side effects following NSAID treatment relative to the number of dogs receiving therapy are available, it must be considered that for many dogs, NSAIDs are a very safe and effective class of analgesic agent. The difficulty lies in identifying dogs that may be at a higher than normal risk of side effects, or animals for which administration of NSAIDs is contra-indicated. Decision making about whether to with-hold NSAID therapy must be carried out following a careful risk-benefit analysis in conjunction with the owner for each individual patient. For example if analgesia is necessary as part of palliative care, it is probable that an increased risk of NSAID side effects will be tolerated due to the requirement for efficacious analgesia in the home environment. The likelihood of side effects should also be used to determine the requirement for blood sampling and biochemical and haematological investigation before starting NSAID therapy. However these are only worthwhile if they will influence decision making about therapy. Due to the high incidence of concurrent disease in animals with chronic pain, blood sampling and testing is recommended before starting therapy in this patient group, but if the owner cannot afford to pay for these investigations, NSAID therapy should still be considered.

Case studies show that the greatest risk factor for NSAID side effects is inappropriate administration, for example administering too high a dose, giving different two NSAIDs at the same time, or combining NSAID and steroid therapy (Lascelles et al. 2005). Other concurrent disease conditions that effect decision making about NSAID therapy include:

- 1) GI disease: Animals with a history of GI ulceration or presenting with GI ulceration are more likely to develop ulceration as a result of NSAID therapy. Administration of gastric protectants, antacids and proton-pump inhibitors (omeprazole) have not been shown to reduce the risk of NSAID related ulceration. Consider other analgesic drugs e.g. opioids, amantadine, tramadol, gabapentin in these animals. If NSAID therapy is initiated, monitor animals carefully for signs of GI complications and warn owners about risks and inform them of the clinical signs associated with GI related complications.
- 2) Renal disease: Reduced renal function is not necessarily a contra-indication to NSAID administration in dogs because renal side effects predominantly occur during periods of reduced renal blood flow. The progression of renal disease must be monitored carefully and frequently in this case population and owners must be warned about the risks associated with NSAIDs and renal function. It is imperative that owners stop NSAID administration if their dog stops eating or drinking, becomes dehydrated or develops GI disease. Water must be freely available to dogs during the day to allow regulation of adequate water intake.
- 3) Liver disease: Dogs with reduced liver function may have altered pharmacokinetics of some NSAIDs depending on the metabolic pathway of each individual drug. Reduced liver function is most likely to cause a reduced rate of NSAID metabolism, risk of drug accumulation and therefore side effects. It is possible to reduce the dose or frequency of NSAID dosing in animals with liver dysfunction, although this can only be done empirically and the dose must be sufficient to provide analgesia.
- 4) Cardiac disease: There is the potential for NSAIDs to exacerbate volume overload, pre-existing hypertension and the risk of thrombo-embolic disease, although these risks have not been quantified. Consider these risks in animals with cardiac disease, and if NSAIDs are administered monitor this patient group carefully, including regular blood pressure measurement. The risk of reduced renal blood flow is greater in animals receiving diuretics or ACE inhibitors, therefore owners must be warned about maintenance of adequate water intake.

- 5) Hypoproteinaemia: Most NSAIDs are highly protein bound, therefore severe hypoproteinaemia has the potential to increase the free fraction of any given NSAID dose, elevating the risk of side effects.

What should you monitor following the start of NSAID therapy?

Following commencement of NSAID therapy it is important to monitor both drug efficacy and the health status of the patient. With respect to health status pay particular attention to the body systems in which adverse effects are most likely (i.e. gastrointestinal, renal, hepatic and cardiovascular systems), however do not neglect to monitor the progress of any underlying disease conditions that may be the cause of chronic pain or any concurrent disease processes. Changes in health status caused by concurrent diseases may influence the risk of adverse events in the target NSAID side effect organs and progression of a disease causing chronic pain may change the requirement for ongoing analgesia.

How frequently should you monitor dogs on NSAID therapy?

Most NSAID related adverse events in dogs occur between 14 and 30 days after starting therapy (Hampshire et al. 2004), however the time course of adverse events are very variable in individual animals. The timing of adverse events also varies with body system. Acute renal failure can manifest two to three days after starting therapy, while deteriorations in hepatic function may only manifest after a few months. Gastrointestinal side effects frequently occur in the first two weeks after starting therapy. Nausea, occasional vomiting and mild diarrhoea are common within this time window and then often improve as the gastrointestinal system adapts to physiological changes caused by NSAID administration. NSAID therapy is recognized to be a risk factor for gastrointestinal perforation, Lascelles and colleagues recommend stopping NSAID administration to dogs that are vomiting because vomiting can be an early presenting sign of gastrointestinal perforation (Lascelles et al. 2005).

The frequency of monitoring should be tailored to the likelihood of side effects in individual animals. More frequent monitoring is indicated in dogs at a higher risk of developing NSAID related side effects, guidance about classifying dogs into high risk and low risk groups for developing NSAID related side effects is given later in this article.

Reassessment of NSAID efficacy and side effects is recommended in all dogs 7-10 days after starting NSAID efficacy.

Warn owners about the clinical signs of NSAID related side effects and instruct them to contact you and stop NSAID administration should any signs develop earlier in the course of treatment. A useful guideline is to advise owners not to give a NSAID dose if their dog has not eaten. Inappetence is a common sign of NSAID related side effects; if inappetence is caused by unrelated concurrent disease it also prevents NSAID administration to dogs at risk of dehydration and hypotension, which predisposes to renal compromise. After 7-10 days it is practical to assess analgesia provided by NSAIDs, and this is a good time point to make a decision about whether adjunctive analgesic drugs are required. Remember that non-pharmacological therapies for osteoarthritis can take longer to be effective (e.g. weight loss, dietary changes such as feeding Hills J/D), therefore requirement for adjunctive analgesic agents may change later in the course of NSAID therapy for pain associated with osteoarthritis.

Following an initial follow-up appointment the frequency of reassessment will vary dependent on the health status of the dog and the underlying condition that is the cause of pain. Young, healthy dogs are at a low risk of NSAID related adverse events, but this patient population rarely requires NSAID therapy for chronic pain. Older dogs are at a higher risk of adverse events, although it is difficult to define when a dog is aged. Consider whether a dog is clinically geriatric (taking into account age,

breed and health status) rather than relying on chronological age alone to classify age status). In dogs that are at a high risk of NSAID related adverse effects regular monitoring at 1-2 monthly intervals is recommended. Frequent monitoring is also recommended in dogs with a progressive or unstable underlying disease condition, particularly with respect to requirement for analgesia and administration of adjunctive analgesic agents. Less frequent monitoring (for example 4-6 monthly intervals) is recommended for dogs at a low risk of NSAID adverse events.

Table 1: Classifying risk of adverse events following NSAID treatment

Characteristics of dogs at a high risk of NSAID related adverse events	Characteristics of dogs at a low risk of NSAID related adverse events
1. Clinically geriatric 2. History of adverse events associated with NSAID administration 3. Concurrent renal, cardiovascular, hepatic or gastrointestinal disease 4. Moderate to severe concurrent systemic disease in other body systems 4. Receiving multiple concurrent drug therapies for concurrent disease	1. Young or adult 2. No concurrent systemic disease 3. Not receiving other concurrent drug therapy

Monitoring of analgesic efficacy

As discussed previously, owners must be involved in the assessment of analgesic efficacy during ongoing NSAID therapy and it can be useful to adopt Client Specific Outcome Measures (CSOM) to objectively monitor changes in specific activities following the start of treatment. Use of CSOM provides an assessment tool that is directly relevant to each specific patient and is therefore more sensitive at detecting improvements or a deterioration in analgesia provided by NSAID therapy. As well as assessing activity and mobility it is important to question the owner about the dog's overall quality of life (QoL), particularly with respect to any concurrent disease conditions that may effect QoL, for example cardiovascular disease that might limit exercise tolerance. Asking the owner to keep a diary about their dog's activity levels, specific behaviours e.g. willingness to get up to greet the owner when they arrive home, changes in temperament, sleep related behaviour and restlessness can be very helpful to determine changes in QoL over time. Together with the owner it is important to determine QoL criteria for the individual patient that may indicate requirement for further intervention. Interventions may involve administration of adjunctive analgesic drugs (for example the addition of amantadine to NSAID therapy (Lascelles et al. 2008)), or for some animals it may be appropriate to consider euthanasia. These intervention criteria can also help the owner determine whether a follow-up appointment is required earlier than the next planned assessment consultation.

Health monitoring during NSAID therapy

Dogs receiving NSAIDs for the management of chronic pain are commonly geriatric and have concurrent systemic disease, therefore it is very difficult to make generalized recommendations for health monitoring. Each monitoring plan must be tailored to the individual requirements of the patient. Target body systems most likely to be associated with NSAID related side effects are the gastrointestinal, renal, hepatic and cardiovascular systems and require particular attention, but that not is to say that all of these systems must be evaluated with specific clinical and biochemical tests at

each evaluation. Although it is not unexpected that dogs with pre-existing disease in one target organ might be more susceptible to NSAID related side effects in that organ remember interactions between body systems. For example dogs with cardiac disease necessitating the administration of diuretics or ACE inhibitors will also be at an increased risk of renal dysfunction with NSAID therapy. Discuss the frequency of monitoring with the owner and explain why their dog might benefit from monitoring at a particular frequency with defined tests. If cost is a limiting factor for on going monitoring then ensure that the owner is fully aware of signs indicative of deteriorations in organ function and carry out re-examination when possible, but at least at 6 monthly intervals.

Table 2: Monitoring function of target body systems following NSAID therapy

Target body system	What should you monitor?	How can this be achieved?
Gastro-intestinal system	Signs indicative of gastro-intestinal ulceration	1. Question the owner about signs of: Vomiting and diarrhoea including whether any signs of blood are present) Nausea (indicated by lip licking, salivation) Inappetance 2. Examine the dog: for signs of gastro-intestinal pain 3. Monitor: bodyweight, PCV and total protein (may provide evidence suggestive of low grade GI bleeding or inappetance)
Renal system	Signs indicative of a deterioration in renal function (acute or chronic)	1. Ask the owner to bring in a urine sample and measure urine specific gravity 2. Question the owner about any changes in drinking behaviour 3. Monitor plasma urea and creatinine concentrations 4. Monitor plasma potassium concentration in animals receiving potassium supplements and animals with concurrent chronic renal failure

Hepatic system	Signs indicative of a deterioration in liver function	1. Question the owner about general behaviour of the dog to detect signs of lethargy 2. Monitor plasma concentrations of liver enzymes (ALT, ALKP) 3. In dogs with pre-existing liver disease or with elevated liver enzymes monitor serum bile acid concentration to obtain a better insight into changes in liver function
Cardiovascular system	Signs indicative of a change in cardiovascular function	1. Question the owner about exercise tolerance 2. Monitor blood pressure in animals with pre-existing hypertension or cardiovascular disease 3. Monitor blood clotting function if the dog is scheduled to undergo surgery for any reason
Other body systems	Reevaluate the status of any other underlying or concurrent disease states	1. Evaluation will be determined by the nature of the disease process

Interventions when changes in target organ function are detected

If an acute deterioration in renal or liver function is detected or signs indicative of gastrointestinal ulceration are detected stop NSAID therapy and instigate appropriate supportive measures. Usually organ function will improve again with treatment and cessation of NSAID therapy. Report adverse events to the appropriate pharmaceutical company and regulatory board to support pharmacovigilance. Provide alternative analgesia for dogs that have stopped NSAID therapy, and consider very carefully whether to restart NSAID therapy once the dog has recovered from the episode. This will depend on the severity of the event, the capability to manage pain with other classes of analgesic drugs and the outcome of discussions with the owner. If NSAID therapy is re-initiated do so cautiously, switch to a different NSAID drug and start therapy at the lowest recommended dose. Frequent monitoring of these patients is required, at least for the first 6 months after starting therapy.

Frequently decision-making about what to do when abnormalities are detected on re-examination are difficult because changes in function are often subtle and deterioration is gradual. There are also no specific criteria for when changes in serum biochemistry indicate that NSAID administration should be stopped. If possible interpret monitored parameters with respect to baseline values measured before the start of NSAID therapy, or with respect to historical data when dogs have been monitored over

time. Be prepared to change the frequency of monitoring dependent on changes in organ function and the underlying disease condition. If mild signs of changes in organ function are detected it is sensible to reduce the NSAID dose to the lowest effective dose and repeat the evaluation one to two months later.

Monitoring NSAID efficacy and organ function are integral to the safe and effective use of NSAIDs for chronic pain management. It is important to tailor monitoring to the requirements of the individual patient and the owner. More frequent and intensive monitoring is required in dogs that are at a higher risk of NSAID related side effects.

Other treatments for chronic pain management in dogs

Paracetamol (acetaminophen and codeine (Pardale V®))

Although the licensed preparation of paracetamol and codeine is authorised for a treatment course of only 5 days, it is used for the long term management of pain in dogs with OA. There are, however, no studies investigating the safety or efficacy of this preparation for management of OA pain. There appears to be the general perception that paracetamol is better tolerated by dogs than NSAIDs but there are no data to support this contention. It is important to be aware that due to a high first pass metabolism of codeine by the liver in dogs (KuKanich 2010), the codeine in this preparation is highly unlikely to be bioavailable and therefore provide analgesia to dogs.

Tramadol

Tramadol is a centrally acting synthetic analogue of codeine that has two different principle analgesic modes of action. Tramadol and O-desmethyl metabolites exert an agonist effect at opioid receptors as well as inhibiting norepinephrine and serotonin reuptake in the central nervous system (CNS) thereby modulating descending analgesia pathways. Despite the fact that it is not licensed for administration to dogs, there has been a huge increase in the popularity of tramadol as a longer-term analgesic for dogs with chronic pain, probably because it is perceived to be safe and devoid of NSAID related side effects. However it is important to be aware that there are very limited data describing the efficacy of oral tramadol for the management of OA pain in dogs. Malek et al. (2012) investigated the analgesic efficacy of tramadol 4 mg/kg three times daily in client owned dogs with osteoarthritis and found it to be equally efficacious to carprofen for some outcome measures. Anecdotally this dose of tramadol is considerably higher than is commonly prescribed for the management of OA pain in dogs, suggesting that many dogs may not receive benefit from tramadol administration at a lower dose, although higher doses (such as 4 mg/kg three times daily) may be associated with dysphoria or sedation in some animals. Interestingly, Malek et al. (2012) also measured plasma concentrations of tramadol and found that plasma concentrations were significantly decreased after two weeks of treatment, indicating that drug metabolism is altered with prolonged dosing. In conclusion tramadol may play a role in the management of OA associated pain in dogs, but further data are required to support dose and dosing interval. Tramadol should not be used in preference to NSAID therapy in dogs, unless NSAIDs are contra-indicated or poorly tolerated by an individual patient.

Amantadine

Amantadine is an oral NMDA receptor antagonist that may therefore be effective in limiting or reversing central sensitisation that occurs as a result of OA. Lascelles et al. (2008) investigated the analgesic efficacy of amantadine combined with a NSAID (meloxicam) in dogs with spontaneous OA and pain that was refractory to NSAID therapy alone and found that pain scores were decreased compared to dogs that continued on meloxicam therapy only. The dose of amantadine evaluated in this study was 3-5 mg/kg once daily. No behavioural, biochemical or haematological abnormalities were noted after 42 days, although amantadine is excreted by the kidneys in dogs and caution is

advised when using amantadine in human patients with kidney disease. These limited data suggest that amantadine may be a useful adjunct to NSAID therapy in dogs with pain caused by OA.

Gabapentin

Due to the likely neuropathic component to OA mediated pain, gabapentin may be a useful adjunct to therapy. The drug is a structural analogue of GABA but its analgesic action is attributed to binding to the alpha-2/delta subunit of the voltage gated calcium channel, thereby decreasing the release of excitatory neurotransmitters. However it is important to be aware that there are no published studies investigating the administration of gabapentin for OA associated pain, therefore recommended dosing regimens are somewhat empirical. Pharmacokinetic studies suggests that a dose of 10-20 mg/kg gabapentin every 8 hours is required in dogs to provide analgesia (KuKanich 2013). Adverse effects of gabapentin include sedation and drowsiness that may limit use in some animals. It is also not recommended to stop the drug abruptly after chronic administration due to the risk of seizures, with the recommendation to reduce the dose of the drug over a period of 1 week (KuKanich 2013).

Neutraceuticals

Neutraceuticals are commonly used for the management of OA associated pain and include products such as glucosamine, chondroitin sulphate, green lipped mussel powder, and dietary supplementation with omega-3 fatty acids. Vandeweerdt et al. (2012) recently conducted a systematic review of neutraceuticals to alleviate clinical signs of OA and reported that there were serious methodological issues with the studies available for evaluation. For example there were limited numbers of rigorous randomised controlled trials, the number of animals included in studies was generally low and there was a lack of standardisation of doses and duration of treatment between trials. These limitations make it very difficult to effectively appraise the evidence base for neutraceutical based treatments but Vandeweerdt et al. (2012) concluded that there was a good evidence base to support a positive treatment effect of dietary supplementation of omega 3 fatty acids in dogs. The proposed mechanism is that omega 3 fatty acids may lower arachidonic acid concentrations and alter the production of eicosanoids to less inflammatory forms. The evidence for other neutraceutical treatments was poor.

Novel agents for the management of OA associated pain

Anti-nerve growth factor antibody

Nerve growth factor (NGF) is an essential growth factor for the development and maintenance of normal nociceptors. At inflammatory sites different cell types produce NGF, contributing to hyperalgesia. Further roles of NGF include increasing the expression of receptors to inflammatory neurotransmitters in the dorsal root ganglion of sensory nerve fibres and stimulating inflammatory cells to release inflammatory compounds. Due to the importance of NGF in nociceptor function a number of human and laboratory animal studies have investigated the analgesic efficacy of antibodies to NGF in the management of OA pain and produced encouraging results. More recently a canine specific anti-nerve growth factor antibody has been evaluated in dogs with OA (Webster et al. 2014, Lascelles et al. 2015). In a placebo controlled trial, Lascelles et al. (2015) used validated clinical metrology instruments and activity monitors to assess pain and activity in dogs with OA for up to 28 days after an intravenous injection of caninised anti-NGF antibody and found improvements in pain scores and activity that were comparable to effects expected from administration of a NSAID, without concurrent side effects. These data indicate the future potential of canine anti-NGF antibody for the management of OA pain in dogs.

2. Intra-articular botulinum toxin A

Botulinum toxin A injected intra-articularly has the potential to provide analgesia in dogs with OA because it inhibits the release of neurotransmitters (e.g. substance P, calcitonin gene related peptide) that are important in the pain pathway. In a relatively small study of 36 dogs with OA, Heikkila et al. (2014) investigated the analgesic efficacy of this treatment and found improvements in pain score and gait in the treatment compared with the placebo group. No side effects were reported resulting from toxin injection. Although sedation or anaesthesia is required to inject into the joint, botulinum toxin A may be efficacious in the management of OA pain for up to 3 months after injection, further studies in larger numbers of animals are required to support these preliminary findings.

Further reading

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