Managing the Pain of Osteoarthritis in Dogs and Cats

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Osteoarthritis (OA) is one of the most common chronic musculoskeletal diseases and causes of lameness in the dogs. The osteoarthritic disease process involves the entire synovial joint, encompassing the synovium, cartilage and underlying bone. Joint failure results from an abnormal mechanical strain causing damage to normal tissue or failure of pathologically impaired articular cartilage and bone under the influence of normal physiological strain or a combination of both. In both cases, the end point is cartilage loss and joint impairment. Osteoarthritic chondrocytes show an altered phenotype characterized by an excess production of catabolic factors, including metalloproteinases and reactive oxygen species(NO). These factors constitute potential therapeutic targets and some new drugs and nutraceuticals have been proposed to promote the return to homeostasis.

It is important to remember that the pain of OA is not felt in the articular surfaces, instead the peri-articular structures such as the inflamed synovium, fibrotic joint capsule, or weak tendons, ligaments or muscle. OA is a disease of the entire joint involving synovitis, atrophy and fibrosis causing pain and progressive degenerative disease.

In recent years the human literature has identified OA pain as maladaptive pain that resembles true neuropathic pain. Maladaptive pain is pain as a disease and involves the creation of peripheral and/or central sensitization.

Pharmacological pain relief

The first line drugs for treatment of osteoarthritis are the Non Steroidal Anti-Inflammatory Drugs (NSAIDs). A number of NSAIDs have been approved for use in dogs and fewer in cats. Generally NSAIDs inhibit one or more steps in the metabolism of arachidonic acid. This class of drugs ameliorates the symptoms of osteoarthritis but also has a role in preventing central sensitization through COX inhibition.

Actions of NSAIDs

Stresses on the joint lead to production of inflammatory cytokines released by synovial cells, chondrocytes, macrophages and fibroblasts. These proinflammatory cytokines, including certain interleukins and TNF-alpha, lead to upregulation of COX-2 enzymes and production of eicosanoids such as PGE2,and the upregulation of matrix metalloproteinases. Normally during metabolism PGs are broken down by enzymes matrix metalloproteinases (MMPs) and aggrecanase. In acute inflammation MMPs increase in number and disrupt the balance of production and destruction in the joint.There is shift toward breakdown of articular cartilage resulting from an imbalance between MMPs and their TIMP inhibitors, leading to thinning and destruction of the cartilage tissue and perpetuation of the inflammatory cascade with PGE2 production and subsequent pain.

NSAIDs block PG synthesis by binding to and inhibiting COX. The major therapeutic and toxic effects of NSAIDs result from this action. The major " safe" NSAIDs are said to be COX2 selective although these do have some COX 1 effects.

Adverse events

Adverse side effects of NSAIDs can include gastric upset, vomiting, diarrhea, inappetence, gastric bleeding, platelet inhibition, analgesic nephropathy, liver and cardiac problems. Inappetence is the most common side effect in cats.

Most adverse events occur within 2 to 4 weeks of commencement of the NSAID and stop soon after drug is discontinued. NSAIDs can cause gastric erosions but unlikely that these would occur without clinical signs. Perforations are most likely caused by concurrent use of steroids and NSAIDs or by using high doses of NSAIDs.

Nephrotoxicity can be seen in patients with pre-existing renal disease, hypotension, hypovolemia, congestive heart failure or diuretic administration. Hepatic necrosis appears to be due to an inherited sensitivity to the molecule used and not a true toxicosis.

Common NSAIDs

Drug	Trade name	Dose	Species
Carprofen	Rimadyl—Zoetis	4.4mg/kg q 24 hours or 2.2 mg/kg q 12 hours	Dogs only
Deracoxib	Deramaxx- Elanco	1-2 mg/kg q 24 hours	Dogs only
Firocoxib	Previcox—Merial	5 mg/kg q 24 hours	Dogs only

Drug	Trade name	Dose	Species
Meloxicam	Metacam, Orocam, Meloxyn—	0.1mg/kg q 24 hrs-dogs 0.05 mg/kg q 24 hrs -cats	Dogs and cats
Robenacoxib	Onsior-Elanco		Dogs and cats

Long term use and safety in OA patients

- Use a veterinary approved drug at label dose—can be used long term and may show improvement in disease from 6 months to 1 year
- Meloxicam and Robenacoxib are metabolized in cats by oxidation not glucuronidation. Long term oral use has been safely demonstrated.
- No one veterinary approved NSAID has been proven to be safer than another.
- Veterinary approved products are safer than non veterinary approved products.

Nutraceuticals that work as well as drugs (and are proven winners)

Omega 3 fatty acids

There are a number of Randomized Controlled Clinical Trials (RCCT) proving the efficacy of Omega 3 fatty acids—fish oil or Marine Oil (Algael Oil) but not flaxseed oil.

Arachidonic acid is the primary substrate for the lipooxygenase (LOX) and cyclooxygenase (COX) enzymes. This fatty acid is derived dietary sources and stored in phospholipids of the cell membrane until needed. AA is a member of the omega-6 fatty acid family. AA can be partly replaced in cell membranes by the omega-3 fatty acid EICOSAPENTANOIC acid (EPA). EPA can be used by the LOX and COX enzymes to produce eicosanoids. When EPA is used by the COX and LOX enzymes, they produce the eicosanoids PGE3, thromboxane (TX) A3 and LTB5, which are less active and relatively anti-inflammatory compared to their counterparts produced from AA.

Omega 3 Fatty Acids can be supplied by supplemented diets (HIll's J/D, Purina JM and RC Mobility Support) or directly supplemented from fish oil capsules or liquid. Dose for supplementation varies but most accepted is:

Injectables

Polysulfated glycosaminoglycans

Adequan (PSGAG) and Cartrophen (Sodium pentosan polysufate) are the 2 products that are available.

Polysulfated glycosaminoglycans (PSGAGs) are a semisynthetic product (derived from bovine trachea) structurally similar to the GAGs found in articular hyaline cartilage. PSGAGs stimulate collagen synthesis and inhibit collagen breakdown as well as decrease pain and inflammation. Several studies have documented positive effects when administering PSGAGs (Adequan) to dogs with hip dysplasia and osteoarthritis. One study found decreased hip laxity in dogs treated with Adequan twice weekly from 6 weeks to 8 months of age compared to age-matched controls. It is recommended to begin treatment as early in the disease process as possible in order to slow the progression of cartilage damage. The strength of evidence for PSGAGs used at the labeled dose is considered high. Dose: 5mg/kg once weekly x 4 to 6 weeks then once monthly in dogs, cats first 4 weeks is the same but 2nd month every other week then once monthly

Cartrophen

Pentosan polysulphate—this product is used in Canada, Europe and Australia. Similar actions to Adequate. Dose is 1ml/33kg once weekly for 4 weeks then once monthly.

Other drugs for chronic/ maladaptive pain

Tramadol

In humans tramadol is known to exert its pain modifying effect through two metabolites; one enhances inhibitory neurotransmitters (serotonin, norepinephrine), and the other (0-desmethyltramadol, or "M1") metabolite is a weak opioid (1/100th the mu-receptor affinity of morphine.) Tramadol has a very short half-life (1.7 hours) in the dog, and it appears that dogs produce very little of the M1 opioid metabolite. Evidence for a pain-modifying effect of oral tramadol remains unknown at this time. Plasma levels in dogs are much lower following oral administration than in humans. One study of oral tramadol reports a statistically significant increase of mechanical threshold levels, but only at the 5- and 6- hour time point. One study does find oral tramadol effective as part of a multi-modal analgesic protocol to control cancer pain, but others have found it (not unsurprisingly) inferior as a solo agent to multi-modal pain management.

Gabapentin

Gabapentin is said to be effective in neuropathic pain states such as post- herpetic neuralgia (shingles) in people. Gabapentin binds to the alpha 2 delta subunit of the voltage-gated calcium channel resulting in the decreased release of excitatory neurotransmitters such as glutamate. It also increases brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. It has also been used in people for fibromyalgia and diabetic neuropathy pain, and restless leg syndrome, and in acute pain states it may reduce the opioid need of some patients.

Gabapentin is used in dogs with neuropathic pain or in dogs who pheotypically appear as if they have neuropathic pain i.e. osteoarthritis. Dosage of this drug is usually 10 mg / kg BI but geriatric dogs may need a decreased dose of 5,g /kg.

Amantadine

Amantadine is an antiviral drug but it also increases concentrations of dopamine in the CNS as well as being an antagonist at the NMDA receptor. It affects central pain sensitization via NMDA receptor and appears to enhance the analgesic effects produce by opioids, NSAIDs and gabapentin. In dogs, one clinical study using 3 to 5 mg/kg once daily in combination with meloxicam showed significant improvement using client-specific outcome measures for activity on day 42 of administration but not on day 7 or 21. This may be a function of dosage frequency as pharmacological data indicate twice daily dosing is more appropriate.

In cats, there is very good oral bioavailability but a short half suggests twice daily dosing in the similar range to dogs. Central sensitization must be present for efficacy to be demonstrated.

Dosage is usually 10 mg .KG BID or in cats 3 to 5 mg /Kg BID to start

Amitriptylline

Amitriptyline and other TCAs are commonly used in neuropathic pain in people. They produce serotonin and norepinephrine reuptake inhibition, some NMDA antagonism, sodium channel blockade and are anti- inflammatory. In the dog suggested dosage is 3-5 mg/kg every 12 hours**.**

Acetaminophen

Contraindicated in cats! It has been used in dogs for a washout period if switching NSAIDs and may be combined with codeine or tramadol. May be beneficial for dogs with renal dysfunction but should not be used immediately postoperative. Even at recommended doses there is some potential for toxicity. Dose: 10 – 15 mg/kg PO q8h; if using long-term (>5 days) consider giving q12h at the lower end of dosing range.

Oral opioids

Maladaptive pain secondary to peripheral nerve damage shows decreased sensitivity to opioids. Oral opioids have a very low bioavailability due to metabolism in the liver. Codeine has the highest bioavailability and is often combined with acetaminophen **in dogs only.**

Dose: 1-2 mg/kg q 4 hours

If combined with acetaminophen dose on the acetaminophen fraction and do not exceed 2mg/kg of codeine.

Cortisone

Corticosteroids are usually the last drug used and are not analgesic but do reduce inflammation. Intra articular injections are common in humans and becoming more common in dogs. Intra articular steroids have been shown to protect articular cartilage in experimental canine OA; however, repeated use may also have deleterious effects on joint tissue from suppression of cartilage matrix synthesis. Benefits usually outweigh risks. Strict aseptic techniques are needed for these injections.

On the horizon

A new EP4 receptor blocking drug, grapiprant, will soon be coming to market. It is rumoured to replace NSAIDs in dogs and will have applications in cats as well. The company producing this drug is Aratana. It should be to market in 2016.

References

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