Multimodal management of canine osteoarthritis

S. Budsberg
Dept Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA. United States

INTRODUCTION

There are several reasons to pursue multimodal therapy for the treatment of chronic pain, such as osteoarthritis. From a physiological stand point, changes induced in the central pain pathways are in part, the result of constant input of noxious signals from the periphery. These changes extend from the dorsal root ganglia to all the higher centers of the brain. From a clinical perspective there is increasing evidence that single modality therapy is not adequate in many cases of OA in dogs. Two common false assumptions about managing pain are that one drug, at one dose, will work for all patients and that pain management is an “all or none” occurrence. However, despite a growing clinical desire to practice multimodal therapy, we must carefully examine the efficacy, safety and cost effectiveness of these new proposed pain protocols.

First, we generally think of multimodal therapy as multiple concurrent drug or pharmaceutical therapy. However in its true sense, multimodal therapy can be any concurrent therapies that might include drugs, physical therapy and diet. We currently promote and use a multimodal management scheme as the most effective non-surgical approach to address OA pain in dogs. This therapy protocol incorporates several components including effective weight control, proper exercise, physical therapy, and analgesic medication. Use of any of these components alone, while beneficial, may not maximize comfort and mobility for the patient. More recently, dietary alterations (N3/N6 fatty acid ratio changes), and augmentation with agents that may provide cartilage modulation have begun to enter the paradigm and may be more commonly recommended as more data is available.

It is important to remember that the clinical need for pain relief in OA is usually precipitated by an acute (“flare”) component instead of by chronic residual pain as perceived by the owner. Flares are characterized by episodic intense pain, and are often provoked by a variety of events including excessive or unusual physical activity. Paradoxically, flares may also occur after periods of inactivity such as after sleeping. Owners of dogs often begin treatment for chronic OA during a flare and then adopt an “as needed” approach to therapy, giving medication only during flare events rather than maintaining a continuous medication program.

To begin logically formulate a pain management plan, we need to briefly review the peripheral and central mechanisms of pain. Peripheral sensitization is defined as enhanced sensitivity of nociceptive nerve endings. Nociceptive pain is evoked by activation of peripheral nociceptors. These sensory receptors are often classified by their size and degree of myelination and according to their responses to mechanical, thermal, and chemical stimuli. During inflammation, a high proportion of somatic and visceral peripheral nociceptors can be sensitized by various mediators including bradykinin, prostaglandin (PG), various leukotrienes, serotonin, histamine and perhaps free radicals. Tissue injury causes alterations in sodium and calcium mediated channels causing the C and Aβ fibers to send action potentials to the CNS. If the injury is persistent, additional recruitment of Aβ fibers and silent nociceptors occurs along with alterations in ion activity. The action potentials are propagated to the CNS. Central sensitization is defined as enhanced sensitivity of nociceptive spinal dorsal horn neurons to sensory stimulation. Central sensitization is triggered by impulses in nociceptive C-fibers. The neural mechanisms that underlie central sensitization are still being explored.

Central sensitization is also evoked by several mediators in the dorsal horn of the spinal cord including PG, nitric oxide (NO), glutamate and other excitatory amino acids and substance P. Ascending pathways transmit pain to the brain. In the brain, complex modulation and processing occur at several sites. Finally a short discussion of the concept of neuronal plasticity is needed prior to moving on to treatment. Neuronal plasticity refers to changes that occur in the established nervous system or more simply stated it is the alteration of physiological response based upon previous stimuli. So, that pain perception by an individual for an identical stimuli may vary each time the stimuli is present. Neuronal plasticity can be caused by injury, inflammation and different diseases. There is a subsequent increase in pain perception by means of either increased excitatory or decreased inhibitory mechanisms. At a molecular level, pain hypersensitivity is the conse-
quence of early post-translational changes, including phosphorylation of membrane bound proteins, as well as, later transcriptional dependent changes in genes at multiple levels along the nociceptive pathway. Neuronal plasticity can result in short-term changes that last minutes or hours, or permanent long-term changes.

MANAGEMENT COMPONENTS

1. Weight Reduction - Weight control is a must when dealing with OA. The vast majority of our patients seen with clinical manifestations of OA are obese. Owner education and proper dietary management must be considered in every case. In many cases, the implementation of weight reduction with rest and exercise modification diminishes or completely alleviates the clinical signs of OA.

2. Nutritional Support - The recent influx of diets on the market with a high N3:N6 fatty acid ratio is adding a whole new area of intervention. It is important to understand that there is an increase in N3 fatty acids in the diet and that specific N3 fatty acids are elevated (EPA and DHA).

3. Exercise modification/Physical Therapy - Protecting the osteoarthritic joint from excessive mechanical stress may limit clinical signs. Use of the joint in a manner that consistently results in discomfort is generally believed to lead to acceleration of cartilage destruction. Most patients with OA are comfortable with light to moderate exercise regimens that do not vary significantly. Enforced rest and exercise modification is different for each animal, but exercise extremes tend to exacerbate clinical signs. Swimming is a wonderful minimal load exercise, and in many parts of the country is available nearly year round to our patients.

4. Pharmacologic Management - Analgesic and antiinflammatory agents are the most common final component in the management of OA. However, there are some risks in using these agents, and one must consider all the possible ramifications prior to their usage. In principle, joint damage leads to an inflammation of the joint tissues which may well result in mediator release and progressive joint destruction. In line with this reasoning, drugs which do interfere with inflammatory processes should reduce joint tissue damage, thus they may be regarded as being of prophylactic and therapeutic value. Additionally, the concept of disease modification in OA is entering the picture of management. Compounds that are being developed to this end are known as disease-modifying osteoarthritis drugs (DMOAD) or structure modifying osteoarthritis drugs (STMOAD). Agents that have been previously called chondroprotective are now considered DMOADs or STMOADs. These drugs can have both effects on the inflammatory cascade and release of mediators and also direct effects on the target tissues (cartilage, bone, synovium).

NSAIDs - Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to control acute and chronic pain in veterinary patients. Osteoarthritis is an irreversible process that results in an end-stage clinical syndrome of the joint. With the testing and marketing of several efficacious non-steroidal anti-inflammatory drugs (NSAIDs) over the last decade, veterinarians are more and more comfortable using these drugs. New discoveries about inflammatory mediators and their interactions in the inflammatory cascade, as well as new data on the biochemical mediators associated with osteoarthritis, have led to increased use of NSAIDs. It is now recognized that there are at least three different cyclooxygenase (COX) enzymes (COX-1, COX-2, and a COX-1 variant called COX-3) which are active in the metabolism of arachidonic acid, and certain NSAIDs may have selectivity in their actions against these isoenzymes. Furthermore, there is data to support that the ratio of COX and lipoxygenase (LOX) inhibition may be important in the improved gastrointestinal safety seen in dogs, and a dual COX/LOX inhibitor has been introduced to the market. However, these drugs are not a panacea with 100% efficacy and 0.0% adverse effects. NSAIDs produce analgesia and toxic side-effects primarily by inhibiting a key enzyme in the arachadonic acid (AA) pathway and cease the production of prostaglandins, most notably prostaglandin E2 (PGE2). The AA pathway is initiated by damage to cell membranes, resulting in the release of prostanoids, which signal inflammation and pain, as well as perform physiologic functions on target tissues. NSAIDs block the rate-limiting step in this pathway at the site of COX, an enzyme which converts arachidonic acid to prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2) through oxidation and reduction reactions. Theoretically, an NSAID that selectively inhibits COX-2 without affecting COX-1 will allow analgesia without the common side effects of COX-1 inhibition, which include altered gastrointestinal and thromboocyte function. Along with the development of different COX specific inhibitors, a confusing COX terminology has developed. Most of the confusion surrounds the marketing of drugs which are described as COX-2 preferential, selective, or highly-selective. These classifications are based upon a completely arbitrary system described by in vitro data. The bottom line is all NSAIDs are COX-2 inhibitors. What is different is how the newer compounds do not concomitantly inhibit COX-1. Thus it is probably better to consider these products as COX-1 sparing. A second area of confusion involves the term ‘coxib.’ Although the term ‘coxib’ is used rather loosely in the literature, often referring to any COX-1 sparing drug, true coxibs are a specific World Health Organization (WHO) designated subclass of NSAIDs. The WHO states that their ‘stem classification system [for drugs] is a working system to help to name new pharmaceutical active substances, rather than a classical pharma-
In addition, extensive data exists which indicate that many of the anti-inflammatory effects of NSAIDs are unrelated to the inhibition of arachidonic acid metabolism. NSAIDs have been shown to inhibit a variety of functions of neutrophils including adhesiveness, aggregation, chemotaxis, degranulation and superoxide anion generations. Additionally there is strong evidence to support that NSAIDs act directly in the spinal cord and higher centers. The mechanisms of how the different cyclooxygenase isoenzymes are involved in the generation of pain sensation are not completely understood and new information is appearing almost every month. Pain is a complex experience involving not only the transduction of noxious stimuli from the periphery to the central nervous system (CNS) but also the processing of the stimuli by the higher centers in the CNS. The most common problems associated with NSAID administration to dogs and cats involve the gastrointestinal (GI) tract but also the processing of the stimuli by the higher centers in the CNS. Most dogs recover with cessation of treatment and supportive care. Renal dysfunction may occur with NSAID administration as a consequence of prostaglandin inhibition. Renal prostaglandin synthesis is very low under normovolemic conditions. When normovolemia is challenged, prostaglandin synthesis is increased and important to maintaining renal perfusion. NSAID use must be considered very carefully in hypovolemic animals. This is especially important to remember with the increasing use of NSAIDs perioperatively for pain management.

When adding additional pharmacological medications to act along with NSAIDs, the terminology of multimodal or balanced therapy appears in the literature. As stated previously, this is really an arbitrary distinction. Tramadol - Tramadol is considered to be an opioid analgesic that is unlike typical opioid analgesics. The mechanism of action is through weak inhibition of opioid receptors, along with interference of the release and reuptake of noradrenaline and serotonin in the descending inhibitory pathways. Central inhibition of proinflammatory cytokines and NF-kB may also occur with tramadol use. No clinical trials have been published demonstrating the effectiveness of tramadol for the treatment of OA in dogs. Although the combination of NSAID and tramadol is commonly used clinically in veterinary medicine, no published clinical trials have demonstrated clinical efficacy of this combination.

Amantadine - Amantadine inhibits the N-methyl D-aspartate (NMDA) receptor. NMDA receptors are found in the dorsal spinal cord. Activation of these receptors is associated with chronic pain. When a and c fibers are chronically stimulated, glutamate is released from the afferent terminal. Glutamate then activates the NMDA receptor in the dorsal spinal cord, resulting in transmission of an ascending impulse along the second order neuron. Despite sound theory suggesting NMDA receptor blockade will result in decreased pain, a truly effective NMDA inhibitor has not been identified for treatment of neuropathic pain in humans. In dogs, one study demonstrated that the combination of amantadine (3-5 mg/kg, once daily) and an NSAID (meloxicam), given for 21 days, provided greater treatment effect than meloxicam alone. This is the first clinical trial, in humans or dogs, to demonstrate an effective analgesic effect of an NMDA inhibitor for the treatment of osteoarthritis.

Gabapentin - It has been speculated that other drugs, such as gabapentin, may also be beneficial adjunctive treatment for osteoarthritis. Gabapentin is structurally similar to gamma-aminobutyric acid (GABA). The mechanism of action is now believed to be through the blockade of voltage-gated calcium channels. No studies have been published evaluating the use of gabapentin for the treatment of osteoarthritis in dogs. Amitriptyline - Amitriptyline is a tricyclic antidepressant that has been used to treat chronic and neuropathic pain in humans. Amitriptyline is thought to act centrally by inhibiting neuronal reuptake of norepinephrine and serotonin. There are no published clinical trials evaluating the use of amitriptyline for the treatment of OA in dogs.

Additional Therapeutic Agents and Chondromodulating Agents

The use of the term “chondroprotective compounds” provokes strong opinions within the medical research community. Rather than spending time debating the merits of this terminology, we will focus on ideas for slowing this process and pragmatic expectations for compounds introduced into this field for treatment. An admirable goal of any therapy prescribed for this disease would be the inhibition of abnormal enzymatic and degenerative processes within cartilage. To this end, alternative terminology has been created to classify therapeutic agents in this area. As stated previously, the agents are collectively defined as slow-acting drugs in osteoarthritis (SADOA). The SADOA products can be subdivided into symptomatic slow acting drugs (SYSADOA) and disease-modifying osteoarthritis drugs (DMOAD). SYSADOA are agents that claim to im-
prove pain or function with a delay (weeks to months) but may have persistent benefits after treatment dis-
continuation. DMOADs are products that claim to prevent, reduce or reverse the cartilaginous lesions of
OA. Agents that have been previously called chondroprotective are now considered DMOADs. Although
there is extensive discussion in the popular press regarding drugs or supplements that may provide a chon-
dromodulating influence, there is little information available verifying treatments that successfully alter
the course of pathologic change. These products include compounds such as glucosamine, chondroitin sulfate,
polysulfated glycosaminoglycans (PSGAG), Pentosan Polysulfate (PPS), hyaluronan (HA), and different
forms of tetracycline analogs.
Polysulfated Glycosaminoglycan - Polysulfated Glycosaminoglycan (PSGAG) is approved for use in dogs
as a disease modifying agent of osteoarthritis (DMOAD). Two studies are published providing information
on the treatment of OA in dogs using PSGAG. One study subjectively suggested a potential positive effect
without statistical significance. The second study provided some additional subjective positive data on im-
provement of lameness but the study group was very small. PSGAG is a heparin analog and its use in an-
imals with bleeding disorders should be avoided. Concurrent use with NSAIDs that exhibit strong anti-
thromboxane (COX-1) activity should be avoided in all patients.
Pentosan Polysulphate - Pentosan polysulfate (PPS) is approved in human medicine to treat interstitial cys-
titis. It is also an antithrombotic/lipidemic agent, and has had recurring popularity as a potential DMOAD.
Two trials in dogs with OA have been published. Both studies were prospective in design, and randomized.
One study subjectively showed a positive effect and the other subjectively showed no positive effect
Nutritional Supplements (Beyond High Omega-3 Fatty acid food)
Chondroitin sulfate, glucosamine hydrochloride, preparations - Two trials were identified describing the use
of compounds, with chondroitin sulfate and glucosamine hydrochloride as major components, for improv-
ing clinical signs associated with OA in dogs. One study subjectively showed a positive effect, while the oth-
er showed no positive effect
Green-lipped Mussel Preparation – Four trials were identified evaluating use of a compound that’s main in-
gredient was green-lipped mussel (Perna canaliculus) for the treatment of OA in dogs. Of the four studies
addressing use of Green-lipped Mussel, three studies suggested mild to moderate improvement, while one
suggested no difference between placebo and treated groups
There are some additional supplements such as P54FP, an extract of the Indian and Javanese turmeric Cur-
cuma domestica and Curcuma xanthorrhiza, and a resin extract of Boswellia serrata which have limited use
and evaluation in dogs and have show some very limited positive subjective data. However, these studies
are very small in scope and limited in design and must be verified by additional clinical trials.