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INTRODUCTION

While considered a very common problem in small animal medicine, osteoarthritis is very likely the most under diagnosed, and misunderstood rheumatic disease in dogs and cats. Part of the problem veterinarians face with OA is that it is a slow, progressive and often insidious problem. In the dog, primary OA is uncommon and OA development always occurs secondary to another joint pathology. The wide range of clinical signs makes OA a commonly misdiagnosed condition. Osteoarthritis has been estimated to affect 20% of the US canine population. This widely referenced estimate, in practical terms, translates to over 10 million dogs. No realistic estimate has ever been made about the number of cats affected. Thus the identification and management of the disease is of the utmost importance to the small animal clinician.

TERMINOLOGY

There is often confusion in the nomenclature during a discussion of osteoarthritis and degenerative joint disease (DJD). It usually becomes unclear to many individuals whether these are the same disease process or different problems. Further confusion arises when considering the term of an “itis, (i.e., inflammatory) and sometimes an “osis”, (i.e., degeneration without inflammation). Without an exhaustive explanation, it is easier to call the process osteoarthritis due to the literature and definitions promoted in humans. Although, using the term degenerative joint disease is technically correct given ones point of view and is sometimes interchanged with osteoarthritis.

DEFINITION

The American Academy of Orthopaedic Surgeons proposed the following consensus definition: Osteoarthritic diseases are a result of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix (primarily collagen and aggrecan), and subchondral bone. Although they may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic factors, osteoarthritic diseases involve all of the tissues of the diarthrodial joint. Ultimately, osteoarthritic diseases are manifested by morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix which lead to softening, fibrillation, ulceration, articular cartilage loss, sclerosis and subchondral bone eburnation, and osteophyte production. When clinically evident, osteoarthritic diseases are characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects.

PATHOPHYSIOLOGY

Osteoarthritis is characterized by articular cartilage degeneration and changes in the periarticular soft tissues (synovium and joint capsule) and subchondral bone. Specifically, the pathologic changes of osteoarthritis encompass articular cartilage degeneration, which includes matrix fibrillation, fissure appearance, gross ulceration, and full-thickness loss of the cartilage matrix. This pathology is accompanied by hypertrophic bone changes with osteophyte formation and subchondral bone plate thickening. Failure to repair the damage affecting the surface cartilage is a distinctive condition of OA. Failure of chondrocytes in injured articular cartilage to restore a functional matrix in spite of high metabolic activity remains a complex and challenging problem. What this says to the clinician at the present time is that there is no treatment regimen proven to arrest or reverse the cartilage degeneration.

TREATMENT GOAL

Current therapy is primarily palliative, aiming to reduce pain and inflammation and maintain or improve joint function without altering the pathologic process in the tissue. Remember, most OA in the dog and cat is secondary to some other pathologic state, and thus the underlying cause must be identified in an attempt to minimize the long-term effects. Certainly efforts are being made to provide treatments which may alter the course of the disease but these therapies are still to a large part unproven.
TREATMENT PLAN

Management of OA should be thought of as a multi-step approach with four to five important components. While some clinicians tend to reach for pharmacologic management alone, this is usually unsuccessful without concurrent management of exercise and weight reduction. Thus, starting to treat a patient with OA requires a lengthy discussion of all aspects of management with the client. Our discussion will follow the typical pattern we use in our practice. Remember, one must examine each case differently, assessing the age, normal activity levels, and, most importantly, the owner’s expectant activity levels of the animal. Success largely depends on the accurate assessment of the client’s expectations for the pet.

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 anti-inflammatory 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. On the other hand, the main symptom of acute joint damage or acute clinical signs of OA is pain, which is a physiological signal to protect the joint from intensive and excessive use. The application of analgesic nonsteroidal anti-inflammatory drugs (NSAIDs) reduces this pain symptom and may, therefore, allow an overriding of this physiological warning signal. Under conditions in which NSAIDs are given and the patient then obviously overuses the limb (such as running a field trial) the use of NSAIDs is obviously destructive for the joint, although it enhances the physiological and psychological well-being. This is precisely why part of our whole treatment protocol specifically involves exercise modification. In addition to the need for analgesic and anti-inflammatory modulation with NSAIDs or similar newer products (COX-1 sparing also known as COX-2 selective agents), additional agents are being tested. These include products which act at the level of cytokines and other mediators. We will not discuss these at this time as they are still in testing. 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).

MULTIMODAL THERAPY

There is a move towards greater use of a multimodal therapeutic approach to treat chronic pain in human medicine, and a multimodal approach has been suggested for the alleviation of chronic pain in veterinary species. The reason for suggesting a multimodal approach for the treatment of chronic pain results from what is now known about the changes induced in the central nervous system as a result of chronic pain, that is, the constant input of noxious signals from the periphery. Once generated, the noxious signal, in the form of an action potential, travels into the dorsal horn of the spinal cord. As in the periphery, the dorsal horn contains multiple transmitters and receptors, both those that have been identified, and putative ones, including peptides (substance P, calcitonin gene related peptide [CGRP], somatostatin, neuropeptide Y, galanin); excitatory amino acids (aspartate, glutamate); inhibitory amino acids (gamma-aminobutyric acid [GABA], glycine); nitric oxide; cholestokinin; arachadonic acid metabolites; endogenous opioids; adenosine; and monoamines (serotonin, noradrenaline). Voltage gated ionic channels are involved in the release of neurotransmitters. Activation of certain sodium channels appears to mediate the release of glutamate, which can bind to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors. A huge breakthrough in the understanding of nociceptive processing came when it was found that the system was plastic - that inputs from the periphery could, via acti-
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viation of a variety of receptors (principally the NMDA receptor) produce changes in the way nociceptive signals were processed in the spinal cord. The characteristics of this receptor are such that with repeated stimulation, it can produce a state of prolonged depolarization in the dorsal horn neuron. This cellular ‘windup’ is thought to produce the state of ‘central sensitization’ via the activation of a variety of second messenger systems, and the production of NO, eicosanoids and induction of immediate early genes. Central sensitization is thought to contribute to injury or disease induced pain by causing amplification of the signals, and by altering processing of sensory information such that previously non-noxious signals are now encoded as noxious. The NMDA receptor however appears to be central to the induction and maintenance of central sensitization, and the use of NMDA receptor antagonists would appear to offer benefit in the treatment of pain where central sensitization has become established (i.e. especially chronic pain). Ketamine, tlete- mine, dextromethorphan and amantadine possess NMDA antagonist properties, among other actions. Recent publications suggest a benefit of using ketamine perioperatively in low doses. Ketamine is not available in an oral preparation, and hence the interest in this study in looking at amantadine, another NMDA antagonist for which there is an oral prepa- ration available. Amantadine has been used for the treatment of neuropathic pain in humans, but as yet, has not been evaluated for the alleviation of pain associated with osteoarthritis. Opioid receptors are well known to be involved in pain states, and the descending serotonergic system is known to be one of the body’s endogenous ‘analgesic’ mechanisms. Tramadol is a synthetic derivative of codeine, which has actions both at the mu opioid receptor, and also facilitates the descending serotonergic system. Tramadol is classified as an opioidergic/nomoaminergic drug. It has been found to be effective in the alleviation of pain associated with osteoarthri- tis in humans, as part of a multimodal approach.

Corticosteroids: These drugs should be limited in use to those dogs in which no other treatment has worked. There is considerable evidence that steroid therapy speeds up pro- gression of OA, and any positive short-term results are negated by long-term loss of the remaining cartilage. Whenever steroids are used, owners must be aware of the proba- ble detrimental side effects. Remember along with iatro- genic induction of Cushing’s syndrome, corticosteroids have been shown to inhibit healing and initiate damage to articular cartilage.

How do we evaluate available information for its validity and applicability?

There are some basic questions that need to be answered for every type of study:
1. Are the results of the study valid?
2. What are the results?
3. Will the results help in caring for my patients?

It is important to understand the concept of a hierarchy of evidence. While every piece of evidence arising from clinical research is important, there are intrinsic quality differences that allow us to determine that some evidence is stronger and can help us determine the best care for our patients.

Weight Loss - What data is available to us?

There are several studies that provide data to support improved quality of life and lameness in the dog.

The data for all is of moderate quality. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies.

Nutritional Support (Functional Foods) - What data is available to us?

High N3 fatty acid ratio diets – Three clinical trials were identified using a diet high in N-3 omega (EPA and DHA) fatty acids. These studies identified assessing potential effects on clinical signs associated with OA in dogs. An overall rat- ing of the strength of the evidence concludes that one can have a moderate to high level of comfort with the results of the aforementioned studies.

Exercise/Physical Therapy - What data is available to us?

There are three studies that examine the effects of exercise on clinical dysfunction associated with OA in dogs. The data for all range from low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned studies.

Pharmacologic Management - What data is available to us?

NSAIDs

Carprofen, Firocoxib, Meloxicam – There are multiple studies to support the efficacy of carprofen, firocoxib, and meloxicam for the treatment of OA in dogs respectively. There is a high level of confidence that the data presented regarding carprofen, firocoxib and meloxicam is valid, and the conclusions of the studies are relevant to our patients. In a practical sense, we can have a high level of comfort that carprofen, firocoxib and meloxicam are effective in treating the chronic pain and dysfunction associated with OA. In cats, one study was found and it too demonstrated decreased pain and dysfunction with administration of meloxicam. This data provides us with a moderate level of confidence the data presented are valid, and the conclusions of the study are relevant to our feline patients.

Cimicoxib, Deracoxib, Mavacoxib and Tepoxalin – There are no peer-reviewed published papers for these approved NSAIDs. Abstracts report deracoxib, and mavacoxib to be effective for alleviating lameness associated with osteoarthritis in dogs. The majority of data on the efficacy of these drugs in chronic pain is not published. There is data for all of them on file with regulatory agencies. There are two experimental studies that show efficacy against acute pain. Thus these data provide us with a low level of confidence data present- ed regarding cimicoxib, deracoxib, mavacoxib and tepoxalin.
are valid, and the conclusions of the studies are relevant to our patients.

Others – There are several products that have one study (usually small numbers) that show some positive effects. These are difficult to evaluate and encompass into our daily practice but they do warrant our attention and continued monitoring for additional data. Examples include intra-articular stem cell therapy, amantadine, elk antler velvet and the original study looking at glycosaminoglycan polysulphate (Adequan®).

Primary Chondroitin and Glucosamine products - Three trials were identified assessing potential effects on clinical signs associated with OA in dogs. Two studies subjectively showed a positive effect, while the other showed no positive effect. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies. But remember we are not saying these products are effective. We are saying that the studies are relevant despite the fact that the conclusions are opposite.

Green-lipped Mussel Preparation – Three trials were identified assessing potential effects on clinical signs associated with OA in dogs. Two studies subjectively showed a positive effect, while the other showed no positive effect. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies. But remember we are not saying these products are effective. We are saying that the studies are relevant despite the fact that the conclusions are opposite.

Tramadol, Gabapentin, and Amitriptyline - What data is available to us? There have been no clinical trials assessing Tramadol, Gabapentin, or Amitriptyline for the relief of painful symptoms associated with any type of chronic pain (such as OA) in dogs or cats. Thus our level of confidence in the use of tramadol, Gabapentin, or Amitriptyline is not measurable.

There are several other products or procedures that show negative or no improvement in chronic pain. Again, these are difficult to evaluate but they may have additional studies that do show a positive effect with larger numbers or different study designs. Thus we might want to monitor the literature for additional data. Examples of this would include extracorporeal shock wave therapy and gold bead therapy.

Address for correspondence:
Steven C. Budsberg
Professor of Surgery - Director of Clinical Research
College of Veterinary Medicine - University of Georgia