CRUCIATE INJURY AND REPAIR IN THE DOG

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Introduction

Disease of the cranial cruciate ligament (CCL) is the most common condition to affect the canine stifle joint. The postulated factors involved in the pathogenesis of CCL rupture are many and include: genetics, breed, age, gender, neutering, ischaemia, obesity, immune mechanisms, tibial plateau angle, intercondylar notch, and local biomechanics. CCL rupture occurs in all sizes of dogs but affects larger breed dogs more often than smaller dogs, and at a younger age. Epidemiological studies have indicated an increased prevalence of CCL disease in breeds such as the Newfoundland, Rottweiler and Labrador retriever, with infrequent occurrence in the Greyhound, Bassett Hound and Old English sheepdog. CCL rupture occurs more commonly in neutered animals, particularly females. It is unknown if this is secondary to abnormal weight gain, as it has been reported that 45.4% of spayed bitches are obese. It is now known that CCL disease has an inherited component in the Newfoundland and Boxer. The classic acute cranial cruciate ligament rupture occurs rarely in dogs. More commonly, slow degeneration of the ligament and osteoarthritis of the joint occurs, due to unknown etiology, before functional failure of the ligament occurs. A high percentage of dogs with unilateral cranial cruciate ruptures subsequently rupture the opposite cranial cruciate ligament. Therefore, there has been significant research into the potential causes of this common problem. Recent genetic evaluations have identified specific genes that may play a part in the development of CCL dysfunction.

Biology

With increased risk of CCL disease in certain breeds and neutered animals, one can ask many questions relating to the nature of the tissue in these animals. Is the CCL "normal" in these animals? For example, is the structure and turnover of the CCL normal? Is the biochemistry of the CCL normal? Earlier studies examined CCL biochemistry, ultrastructure and biomechanics of CCLs from two at-risk breeds (Labrador and Golden Retriever) and compared these to a low risk breed (Greyhound). Collagen fibril diameters were measured and it was found that the mean fibril diameter in the Labrador is significantly smaller than that of the Greyhound. Markers of collagen turnover in CCLs in these breeds of dog have also been assessed. These data suggest that collagen turnover in CCLs from at-risk breeds is increased. Recent work has focused on the cell morphology. Alterations in cell morphology may alter the ability of cells to produce healthy matrix and repair damage through disruption of collagen production. There are marked regional variations in the cell morphology of the canine CL complex. Additionally, chronic inflammation has been suspected in the pathophysiology of CLL dysfunction.

<u>Conformation biomechanical perspectives</u> – In recent years, the tibial plateau has been a subject of much debate. Does an excessive slope to the tibial plateau contribute to the incidence of CCL disease? One study suggests that dogs with CCL rupture do have an excessive slope to the tibial

plateau. However, other studies have failed to substantiate these data. Interestingly, one recent study has raised the possibility of tibial tuberosity conformation being a risk factor for CCL disease. Another study looked at a variety of conformational variables and suggested that cranial angulation of the proximal portion of the tibia, excessive steepness of the tibial plateau, and distal femoral torsion appeared more likely to be associated with CCL deficiency than femoral angulation, tibial torsion, intercondylar notch stenosis, and increased inclination of the patellar ligament. Currently there is no complete understanding of the reasons why CCL fail in dogs.

Management of CCL dysfunction

Conservative Management - Exercise restriction, weight loss, and physical therapy has been recommended for treatment of cranial cruciate rupture. It seems to be more often attempted in small dogs (<10 kg) and cats. In this author's experience, however, lameness does not often completely resolve in these animals and they commonly return for surgery.

Surgical Management - Currently recommended surgical techniques can be roughly divided into two groups; techniques that change the mechanics of the stifle to achieve stabilization, and techniques that act to restrict drawer motion with a physical device. The former group includes TPLO, TTA, and various modifications of the tibial wedge osteotomy. The latter includes long-described extracapsular suture techniques and intracapsular reconstructive techniques. Currently, some form of Tibial Plateau Leveling Osteotomy (TPLO), Tibial Tuberosity Advancement (TTA), and Extracapsular Suture, including the TightRope®, are the three most widely accepted treatment methods. No perfect treatment for cruciate rupture has been identified in the dog.

Extracapsular stabilization with sutures is still a useful technique with proven positive outcomes. The most common methods employ a synthetic suture passed around the lateral fabella and through the tibial crest or employ bone anchors in the distal femur and proximal tibia. In three recent publications, extracapsular stabilization was compared to TPLO and was found to provide significant improvements in function after surgery but was inferior to the TPLO. In a retrospective study, complications were recorded in 63 of 363 lateral fabellotibial suture surgical procedures (17.4%) and 7.2% required a second surgery to manage the complications. A second more recent study confirms an infection rate at 17 %. Factors significantly associated with a higher rate of complications were high body weight, propofol induction agent and young age of dog at the time of surgery. These findings are similar to other previous retrospective studies of extracapsular procedures including the TightRope® procedure.

Tibial Plateau Leveling Osteotomy (TPLO) has been applied to clinical cases for over two decades now. The TPLO mechanically reduces cranial tibial thrust in the weight-bearing phase by "leveling" the tibial plateau. It is important to note that there is no difference in tibial plateau angle between dogs that rupture or do not rupture their cruciate ligaments, but that correction in the angle biomechanically stabilizes the stifle. The overall complication rate after TPLO in 1000 cases was 14.8% (6.6% major), which included 2.8% meniscal injury and 6.6% infection. TPLO may be combined with tibial wedge osteotomy for dogs with complex tibial deformities or exaggerated tibial plateau angles. Earlier studies found a much higher complication rate, which is to be expected as the procedure was being refined. Recent studies have shown TPLO to be effective in small dogs and may be more efficacious than extracapsular repair in small dogs.

The Tibial Tuberosity Advancement (TTA) seeks to eliminate tibial thrust by positioning the patellar tendon perpendicular to the shear forces in the stifle, resulting in the same redirection of vector force as the TPLO. TTA theoretically relieves patellar ligament tension whereas TPLO may increase it. The overall complication rate after TTA has been reported to be between 25 and 31.5%. Three published studies reflect the early clinical experiences with the TTA technique. These three studies (249 cases) report a total overall complication rate of 20.0%-59% in cranial cruciate ligament deficient stifle joints repaired using the TTA. The major complications were between 12-38%, with a re-operation rate of 11.3-14.0%. Again, as with the TPLO, these studies were done early in the use of this procedure and the complication rate is probably much lower now. Recent publications suggests that a TPLO may be more effective at returning dogs to normal function compared to TTA, however more data is needed.

Meniscal Removal or Release

Medial Meniscal injuries are quite common following rupture of the cranial cruciate ligament. An incidence of 50-70% of meniscal injury, identified at the time of surgery for CCL injury, has been reported in dogs. The medial meniscus is most commonly damaged as it is more firmly attached to the joint capsule and medial collateral ligament than the lateral meniscus. However, lateral discoid tears and longitudinal tears of the lateral meniscus are reported. The lateral meniscus is attached to the femur by a ligamentous attachment and when cranial drawer occurs in a CCL deficient knee, the lateral meniscus remains with the femur and is loaded normally. However, the medial meniscus moves cranially resulting in the caudal horn being loaded abnormally. The management of these injuries usually involves removal of the damaged area. Meniscal resection induces osteoarthritis. Any surgical intervention on menisci should be carefully considered. Meniscal injuries are associated with pain necessitating surgical intervention. Resection of meniscal tears improves short-medium term outcome but carries a poorer long-term outcome. Damage can also occur following surgical treatment of a cruciate injury. Currently, a more perplexing issue is the practice of the meniscal release (either transection of the ligament of the caudal pole of the medial meniscus or the transection of the mid body of the medial meniscus) as part of cruciate ligament rupture management in conjunction with a TPLO or TTA. Furthermore, some surgeons have recommended meniscal release as the preferred method of primary treatment of any meniscal pathology.

Why Meniscal Release?

Late meniscal injury has been reported and is believed to be the result of continued cranial tibial thrust. Postliminary (“late”) meniscal injuries are reported in dogs. These injuries have been reported to occur from 3 weeks to 9 months post-operatively, with an average of 6 months after the first surgical procedure. Dogs with this injury will typically present as having had a normal recovery after the first surgery and then present with an acute lameness 6 weeks to 6 months in the previously operated limb. With rupture of the cranial cruciate ligament, there is loss of the passive restraint to the cranial tibial thrust allowing the femoral condyle to displace caudally over the tibial plateau. The medial meniscus is especially susceptible to injury due to the rigid attachment of the caudomedial meniscotibial ligament. This attachment essentially holds the meniscus in place while the femoral condyle crushes the caudal horn with excessive tibial thrust.

It has been shown that meniscal release results in increased contact stress between the femoral and tibial condyles, thus predisposing the cartilage surfaces to increased stress and likely subsequent degeneration and formation of osteoarthritis. Recently the TPLO and TTA have become popular surgical interventions for the cranial cruciate ligament deficient stifle aimed at neutralizing cranial tibial translation. Such procedures have two schools of thought behind them but neither has strong clinical data to support their claim. One group feels that there is a need to release the medial menisci as there is still movement between the femur and tibia and thus the meniscus is at risk, while the other group feels that those procedures are protective of the meniscus through elimination of the caudal pole impingement of the meniscus, thus obviating the necessity for the concurrent release.

Early anecdotal reports stated that without meniscal release, dogs undergoing TPLO procedures had a high rate of subsequent medial meniscal injury. These statements were never confirmed in any published peer review reports, yet the practice of meniscal release grew over the years. The actual incidence of meniscal injury following cruciate rupture is unknown. There is some data from studies following initial surgical visualization. Data collected from other methodologies of repair (extracapsular sutures and intraarticular graft replacements) suggested that about 12 percent of cases had subsequent meniscal injuries which required repair. However, dogs with clinical problems were the only ones who had second surgical explorations, thus the actual number may be higher. A recent relatively small study suggests that there is between 3% (joints explored with arthroscopy) and 10% (joints explored with an arthrotomy) of cases of subsequent medial mensical injury without meniscal release after TPLO. However, no large prospective, randomized, clinical trial has been completed evaluating the effects of meniscal release on the rate of secondary meniscal tears in surgically stabilized cranial cruciate deficient stifles. Recent retrospective studies indicate that the meniscal release procedure does not prevent secondary tears from occurring. These data counter earlier data suggesting the procedure was needed. Thus the conundrum facing us today do we release or leave the apparently normal meniscus alone? In vitro studies have produced data that do not answer all the questions and have some conflicting results. Not surprisingly, in vitro canine cadaveric data has shown that meniscal release has some significant effects on the joint. In one study, radial transection of the medial meniscus resulted in significant alterations in pressure magnitude and distribution through the axially loaded stifle joint. Other data found an increase in pressure on the cartilage of the medial tibial condyle with meniscal release and TPLO. Also, meniscal release was equivalent to caudal pole hemi-meniscectomy in regards to load-bearing, implicating the loss of hoop tension for this high and non-uniform pressure distribution. The effect of meniscal release on stifle joint stability was not different from caudal pole hemimeniscectomy, suggesting that the former had no advantage over the second in regards to contributing to stifle joint stability. Meniscal release also caused greater cranial tibial thrust in the CCL deficient stifle joint compared to the intact stifle joint in cadaveric limbs. The limited *in vivo* data strongly suggested that release of the medial meniscus does induce significant pathological changes in the stifle joint or in the function of the limb.

Conclusions

CCL dysfunction is very common in dogs. The disease process is complicated and rarely involves a supra-physiologic injury. Thus bilateral CCL rupture is not uncommon. Regardless of the technique used, extracapsular techniques or tibial osteotomies should result in improvement

in the surgical population following surgery. No current technique will halt the progression of osteoarthritis.

Obesity and Musculoskeletal Problems

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Every day we are seeing more and more fat pets in our hospitals. Yet the realization and acceptance of the problem has been paradoxical. Our patients are heavier yet obesity is not often noted as a diagnosis, perhaps reflecting the perception of practitioners that obesity does not constitute a disease state.[1] Perhaps we should step back and remember the definition of a disease which is "a pathological condition of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress, and characterized by an identifiable group of signs or symptoms." I think it easy, although perhaps debatable, to list obesity as a disease. Excess body weight has been associated with or may exacerbate a wide range of potentially serious conditions; not limited to locomotor and musculoskeletal problems, respiratory dysfunction, hypertension, cardiac disease, diabetes mellitus, and neoplasia.[2-16] Adipose tissue was once thought of a passive fuel depot, it is now recognized as an active endocrine organ that communicates with the brain and peripheral tissues by secreting a wide range of hormones and protein factors often collectively called adipokines. Examples include adipokines such as leptin, adiponectin, and several cytokines including TNF-alpha, and IL-6.[17]

The impact of obesity on osteoarthritis (OA) and musculoskeletal dysfunction in dogs and cats is well documented. In this lecture we will discuss the known associations between obesity and musculoskeletal problems. Then we will discuss the disease osteoarthritis, the most common long term medical consequence of obesity on the musculoskeletal system.

Numerous studies conclude that obesity negatively affects the canine musculoskeletal system. One of the most important studies documents the effects of excess weight in the development of osteoarthritis in Labrador Retrievers.[11-16] This seminal study has provided a wealth of data that is useful in treating our canine patients. While the results of this study are repetitively referenced, it is important that we spend some time reviewing the findings. Forty-eight puppies were paired by sex and body weight within their litter to participate in the study. Puppies came from 7 dams and 2 sires. At eight weeks they enrolled one dog from each pair in the control fed group and one dog entered the limit fed group. These dogs were then followed for life. Collected data included effects on the development of osteoarthritis (OA) in multiple joints and on the causes, time and predictors of death and ultimately life-span. Briefly, the prevalence and severity of OA in several joints was less in dogs in the limit fed group compared to the control fed group. Specifically in reference to the coxofemoral joint, limit (restricted) feeding delayed or prevented the development of radiographic signs of hip OA. The slowing of OA had a favorable affect on both the duration and the quality of life. The median life span of the control fed dogs was 11.2 years, while the limit fed dogs had a median life span of 13.0 years. Declining lean mass was predictive of death, most significantly at a year prior to death. Additional data has provided support to suggest nutritional over-supplementation (overfeeding) contributes to several developmental bone disorders including hip and elbow development and osteochondrosis.[10, 11] There is one report that found weight to be a predisposing factor in humeral condylar fractures,

cranial cruciate ligament ruptures and intervertebral disc disease in cocker spaniels.[18]

In cats there is a paucity of information linking orthopedic disorders and obesity. Limited data indicates that cats with increased body condition scores are nearly 5 times more likely to develop lameness requiring veterinary care.[19] Furthermore, there is an association between overweight cats and the development of Salter I fractures of the proximal femoral physis (slipped capital femoral epiphysis) without apparent trauma.[20,21] Finally heavier cats are potentially more susceptible to cranial cruciate injuries.[22]

Despite the different effects obesity has on the musculoskeletal system, the overriding long term consequence is OA. It is generally accepted that the most effective non-surgical approach to address OA pain in any diarthroidal joint is multifaceted including effective weight control, proper exercise, physical therapy, and analgesic medication, which have already been discussed today at length in other lectures.

Interestingly our calls for change are not new. Joshua[23] wrote in 1970 about obesity and said the role of the profession was to prevent rather than cure obesity. Dr Joshua went on to say that people recognized the dangers of obesity in their children and themselves and they must be made to face the problem in their pets. These statements echo the saying “The more things change, the more they stay the same”.

Additionally a couple of recent articles deserve mention and are free online. The first is a well written about obesity in our patients and the real physiologic it has on them..[24]The second one is an interesting article that provides an overall look at some of the recent discussions about canine obesity and osteoarthritis. [25]

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Antimicrobial Prophylaxis in Orthopedic Surgery

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Definition and History: A working definition of antimicrobial prophylaxis in surgery is the administration of an antimicrobial drug to a patient, in the absence of infection, prior to surgery. The history of the use of these agents during surgery is interesting and reveals many of the problems which occur with their use. When antimicrobial agents became available to surgeons, they did not provide the panacea for prevention of all surgical infections. In fact, a twenty-year analysis indicated that no significant alteration of infection rates had occurred since the advent of prophylactic antimicrobial usage in human surgery. The study went on to identify the following misuses:

1. Excessive use in clean surgical procedures
2. Faulty timing of administration of the antimicrobial agent
3. Continued use beyond the time necessary for benefit.

Today, unfortunately, some of these misuses are still occurring in veterinary surgery.

The reason that misuses still occur in our profession is partly due to the limited amount of data based on clinical studies in veterinary medicine. Most of the studies available do not justify the use of prophylactic antibiotics in the study populations examined. Despite this fact, it is safe to say that a majority of surgeries done in veterinary practices are performed with antimicrobials given to the patient.

Wound Infections: In the evolution of wound infections, there are three main components. These are bacterial inoculum, bacterial nutrition, and impaired host resistance. The mere presence of bacteria is less important than the level of bacterial growth. Therefore, the goal of the surgeon is to maintain a favorable balance between patient and bacteria. It is important to remember that proper surgical technique and proper patient preparation, strict adherence to aseptic technique and application of atraumatic surgical technique are far more important in the prevention of infection than the use of antibiotics.

Patient Profile for Antimicrobial Prophylaxis: The next question to ask is "In which patients should I use antimicrobial prophylaxis?" There are no hard and fast rules to follow but the following examples can be used for some general guidelines. Many orthopedic procedures are defined as clean surgical wounds, and, in general, the use of prophylaxis is difficult to justify. Important factors to consider when giving antibiotics prior to surgery include: anticipated duration of the operation (degree of contamination), local wound factors favoring infection (e.g., extensive tissue trauma, placement of large implants) and systemic factors favoring infection (e.g., concurrent infections, diseases suppressing immunity).

Procedures in which it is difficult to justify giving antibiotics include:

1. Arthrotomies including removal of endochondral ossification defects or open joint reductions
2. Arthroscopy
3. **TPLOs ? or TTA's?**

Procedures which can be more easily justified for the use of prophylaxis are:

1. Total hip replacement
2. Complex multiple fractures
3. Open fractures
4. Systemically comprised patients

Timing of administration: Maximal therapeutic concentrations of the antibiotic must be present in the tissue at the time of contamination (i.e. beginning of surgery)!!! Experimental work has demonstrated a short, early period in which "decisive biochemical interactions" between the microorganisms and the host tissue occur. During this time the development of the primary bacterial lesion is susceptible to the action of parenterally administered antibiotics. The major effect is in the first minutes of the contamination and no effect is seen if antibiotics are given 3 hours after contamination has begun. Thus, if given intramuscularly, administer 30 minutes prior to your incision. If given intravenously, administer 15 minutes prior to the incision. Repetitive dosing during surgery should occur depending on the antimicrobial given. As an example with a first generation cephalosporin (cefazolin) every 2 to 2.5 hours is adequate according to published data. Serum half-life has been used as a guideline for this dosing, but it is not consistent with concentrations in the tissue (i.e., the drug is given at every half-life).

Choice of Antibiotics: No single antibiotic agent or combination can be relied on for effective prophylaxis in all the various settings found in surgery. Antibiotics used in surgery should be aimed toward the expected contaminating bacteria. The antimicrobial agent should also be bactericidal, have a low side-effect profile, be cost effective and be parenterally administered. In orthopedics, the expected contaminating organism is a staphylococcus from the skin of the patient, which usually produces beta-lactamases. Thus cephalosporins, semi-synthetic beta-lactamases, resistant penicillins, and clindamycin are acceptable choices.

Duration of Antimicrobial Prophylaxis: The use of antibiotics beyond the immediate postoperative period is unnecessary. * 6 – 12 HOURS POSTOPERATIVE * There is strong evidence that use of antibiotics for days after surgery is not only unnecessary but can actually be detrimental to the patient. Now I know there is some conflicting data with TPLO's that may disagree with that and we will look at the data.

Potential Advantages: The most obvious advantage is the prevention of infections. This, in turn, will decrease morbidity and mortality from surgery and decrease hospital stay and cost. Ultimately, this pulse form of usage can actually reduce total antibiotic use in surgical patients.

Potential Disadvantages: In veterinary medicine, we do not look critically at the potential disadvantages of antibiotic use. The most clinically important and seldom considered disadvantages are:

1) **The development of resistant organisms**.
2) Allergic reactions also are not considered, unless it entails a life threatening situation.
3) Non-allergic toxic reactions such as nephrotoxicity of aminoglycosides.
4) Costs, remember the cost of each dose given to a patient in which antibiotics are not necessary should not be overlooked.

Case Example

A simple example I always use that will hopefully help you make your decision on antibiotic use is this:

You have an infection rate of 4 % for a given procedure. You are attempting to decrease that rate to 2 %. To institute your plan, you perform 100 of the aforementioned surgical procedures. All animals receive a prophylactic antimicrobial drug. After evaluating all the patients, you discover that you have decreased your infection rate to 2%. Thus you have accomplished your goal. Now the question arises, was it worth it?

(i.e. Are you willing to give 96 dogs antimicrobial agents which are not benefitting them to prevent an infection in 2 animals?)

TREATMENT OF OSTEOARTHRITIS IN DOGS AND CATS

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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. The exact number of dogs affected with OA is well over 20% and in cats over the age of 10 it is estimated to be over 80%, probably closer to 95%.

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 now 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 necessary 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.
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).

Monoclonal Antibodies, specifically Anti-Nerve Growth Factor, are now making their way through clinical testing in both the dog and the cat. There is some exciting new clinical data supporting their use in our canine and feline OA patients.

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 because 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-amino-butyric acid [GABA], glycine); nitric oxide; cholesystokinin; arachadonic acid metabolites; endogenous opioids; adenosine; and monoamines (serotonin, noradrenaline).

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 activation 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 directly contributes to injury or disease induced pain. This is done 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. Also, 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). 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.

Choosing the Right Combination of Therapies

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.

Nutritional Support (Functional Foods) - What data is available to us?
High N3 fatty acid ratio diets – Several 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 rating of the strength of the evidence is moderate to high.

Exercise/Physical Therapy - What data is available to us?
There are limited studies that examine the effects of exercise on clinical dysfunction associated with OA in dogs. The studies suggest some improvements with different therapies. The data for all range from low to moderate quality and strength.

Pharmacologic Management – What data is available to us?
NSAIDs
Carprofen, Firocoxib, and Meloxicam – There are multiple studies to support the efficacy of carprofen, firocoxib, and meloxicam for the treatment of OA in dogs. 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.

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 ®).

Amantadine, first recognized as an anti-viral agent, has gained popularity for the treatment of chronic pain disorders via inhibition of NMDA receptors. NMDA receptor activation, secondary to chronic stimulation of A delta and C fibers, is believed to be the primary component leading to "spinal windup". One study compared the effects of adjunctive amantadine with meloxicam in a population of dogs with chronic OA refractory to NSAID therapy alone. Dogs treated with meloxicam in conjunction with amantadine had improved client-specific outcome measure scores and overall activity compared with the administration of meloxicam alone.

Tramadol is an opioid analgesic acting at the μ receptor while inhibiting serotonin uptake and norepinephrine reuptake. Tramadol also inhibits central pro-inflammatory cytokines and influences various neuronal cation channels while locally decreasing IL-6 and substance P. There is only one single study in dogs with OA evaluating the effects of oral tramadol in a blinded study using positive and negative controls. There was significant improvement noted in the positive control group (carprofen, 2.2 mg/kg twice a day) and tramadol (4 mg/kg 3 times a day) group compared with the placebo (administered 3 times a day) group using the canine brief pain inventory questionnaire. However, several other outcome measures in this study showed no improvement over placebo or baseline during the administration of tramadol. Thus, the limited data from this study is difficult to assess in terms of recommending tramadol use in dogs with

OA as a monotherapy.

Gabapentin, is structurally similar to the central inhibitory neurotransmitter GABA (gamma-aminobutyric acid). GABA is synthesized from glutamate, an excitatory neurotransmitter. During periods of chronic pain, there is up-regulation of glutamate and subsequent NMDA receptor activation with a relative decrease in GABA concentration. This results in loss of an endogenous feedback mechanism and an uninhibited nociceptive pathway. Though gabapentin's mechanism of action was initially assumed to be through GABAnergic transmission, the therapeutic effects are believed to be moderated through the alpha2 subunit of voltage-gated calcium channels resulting in central analgesia. To the author's knowledge, there are no available clinical or experimental studies evaluating the role of gabapentin in treatment of OA in dogs.

Biological Products

Anti-Nerve Growth Factor Antibody - As a member of the neurotrophin family, nerve growth factor (NGF) can bind the general neurotrophin receptor p75, as well as its high affinity cognate receptor, tropomyosin-related kinase (Trk)A. The NGF-TrkA pathway in particular appears to be critical in driving acute and chronic pain. Recently, canine and feline versions of anti-NGF antibodies have been developed. Two recent studies, where dogs with OA were treated with anti-NGF antibodies, yielded promising results. Additionally, there is one study in cats also showing promising results.

Current regenerative technologies for musculoskeletal injuries consist of three general categories. The first category is adult mesenchymal stromal cells, also known as mesenchymal stem cells (MSCs). MSCs are cells with high proliferative and self-renewal capabilities, are adhesive to plastic surfaces, show specific cell surface proteins, and have potential to differentiate in at least three lineages, including bone, cartilage, and adipose tissue. The second category is plasma-based products, such as Platelet-rich plasma (PRP). PRP consists of a pool of signaling proteins including growth factors, cytokines, and other adhesive proteins involved in healing mechanisms. The list is not exhaustive. Autologous and, more recently, allogenic stem cell therapies have shown some limited positive results in clinical trials when given to dogs with OA. Additionally, studies of limited size and scope have also shown initial positive results for autologous plasma/platelet treatments in dogs with OA. There is no clinical data available on conditioned culture media (CM).

Primary Chondroitin and Glucosamine products – There are conflicting results in limited clinical testing. It is difficult to say these products are effective or not.

Green-lipped Mussel Preparation – Three very small trials were identified using a compound with the main ingredient green-lipped mussel (Perna canaliculus) for the treatment of OA in dogs. While all studies subjectively showed a positive effect, the quality rating for some of the studies suggested some uncertainties exist relating to the scientific quality

Several other products or procedures 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.

Feline Osteoarthritis

Clinical Presentation

There are several reasons for under-appreciation of the clinical significance of DJD. First, the clinical manifestations of the problem in cats are more difficult to identify. Cats with DJD do not act like dogs affected by the same disease. Cats are not subject to the wide range of juvenile joint dysplasia conditions that result in a high occurrence of secondary osteoarthritis in young pure breed dogs, making this a very common finding in this species. Mobility disorders are much more readily identified in dogs where the owner is characteristically present while the animal is exercising and able to recognize lameness or changes in the activity pattern. Lastly, the radiographic appearance of an osteoarthritic joint in the cat is much subtler than the dog with less obvious proliferative osteophyte formation. This may result in the problem being overlooked or dismissed as clinically insignificant. Very little work on the assessment of DJD joint disease pain has been performed in cats. However, it appears from early work that an approach, similar to that in dogs, is likely to be most successful. That is, owners need to be centrally involved in the process. The difficult part of assessment of DJD pain in cats is that the activities that are altered by osteoarthritis are less fully understood than in dogs. A recent study of 28 cats with osteoarthritis showed that overt lameness was not the most common clinical feature. Instead, features like jumping up, jumping down, height of the jump, general movement, "grumpiness" on handling, and seeking seclusion are likely to be activities and behaviors that should be followed.

Diagnosis

Given the aforementioned discussion, how do we develop a methodology to diagnose DJD in cats with high sensitivity and specificity? First, the possibility of the diagnosis must be on the rule out list for any middle to older age cat presenting for changes or decreases in activity, or behavioral changes. Careful and complete history and physical examination is a must. These activities are time consuming and often overlooked in a busy day of seeing patients. If lameness or stiffness are noted, or it was reported that the cat has altered jumping activities (both height and frequency), then DJD must be very high up on the differential diagnosis list. On physical examination, pain or decreased range of motion in a joint are classic markers for DJD. If there is suspicion of DJD, radiographs are the next diagnostic test to be considered. If no specific joint can be detected in the forelimb, consider taking films of the elbow first, then shoulder and finally the carpus. If no one joint can be singled out in the hind limb, consider taking films of the hips, followed by the tarsus and stifle. Also consider radiographs of the thoracolumbar spine. While the significance of radiographic findings of DJD have been questioned in the past because of the lack of associated signs, it should be argued that the lack of correlation is due to the inability of the clinician and owner to appreciate the signs being shown. While three different studies found low correlation, the reasons for this are most likely that feline gait/lameness and mobility dysfunction is much more difficult to identify and that either signs were overlooked in the retrospective populations—or that overt lameness was not one of the main manifestations of the disease in cats. As owner assisted outcome measure tools become better defined and validated, it

is very likely that the correlation between radiographic changes and clinical changes will dramatically improve.

There is a wonderful article in
Feline Chronic Pain and Osteoarthritis
By Beatriz P.Monteiro
Veterinary Clinics of North America: Small Animal Practice
Volume 50, Issue 4, July 2020, Pages 769-788

I highly recommend you obtain this article if you are at all interested in treating cats with OA.

Treatment

Weight loss – No specific clinical trial data is available to evaluate but significant data on obesity strongly shows the benefits to weight loss.

Dietary Management - As with the dog, high N-3 fatty acid ratio diets are starting to become available, yet data is limited to strongly support their use. While these diets may be effective, none has been evaluated to any significant degree. Part of the reason for the lack of evidence-based information about treatment of feline DJD-associated pain is the lack of validated outcome measures, and partly because of a lack of understanding of how to diagnose the disease, as well as lack of understanding about its causes.

Physical Therapy – The use of "Environmental enrichment" to promote physical and mental stimulation in cats has started to become more commonplace. Traditional physical therapy and exercise modification is often difficult in cats given their personalities.

Pharmacologic Therapy –

NSAIDS - Currently, only NSAIDs have data showing a beneficial effect (pain alleviating and mobility enhancing) in painful feline DJD (Meloxicm and Robenocoxib). Meloxicam has a long-term label claim in Europe. Concern about use of NSAIDs in cats, especially on a chronic basis, is generally centered around the perception that NSAIDs are metabolized more slowly in cats than dogs. Most NSAIDs are cleared from the body through hepatic metabolism (often primarily glucuronidation) and then biliary and/or renal excretion of the resultant polar metabolites. Given the known propensity for reduced glucuronidation of drugs in cats compared with other species, differences in NSAID disposition between cats and other species might be expected. Aspirin, and carprofen have relatively prolonged elimination half-lives in cats compared with dogs. In contrast, similar or even reduced drug elimination half-lives are observed in cats, compared with dogs, for drugs cleared by oxidative enzymes, including piroxicam and meloxicam. Presence of alternate metabolic and non-metabolic pathways for drug elimination may compensate for slowed glucuronidation of NSAIDs in the cat. Chronic painful disease demands repeated administration of analgesic drugs, and there is little current information on the pharmacokinetic (PK) and toxic effects of repeated administration of NSAIDs in cats. A good, rational discussion of the use of NSAIDs in cats was published in the Journal of Feline Medicine and Surgery (2010) by Sparkes et al. It is available free online.

Tramadol - There is one study that has been shown to decrease central sensitization and to improve motor activity and global QoL in cats with OA (2–4 mg/kg every 12 h, for 5–19 days). While the data is limited, it does seem to show the treatment to be safe and provides some level of analgesia. However, oral tramadol is bitter, making it unsuitable for many cats. Remember, with all oral medications in cats, treatment is unacceptable if there is forced pilling chronically. These activities can impair owner-cat bond and all that is entailed with that daily potential physical and mental trauma.

Gabapentin – One study showed improved owner-identified impaired activities (CSOM) that in a small group of client-owned cats, treatment with gabapentin at 10 mg/kg, every 12 h for 2 weeks when compared with placebo. However, cats receiving gabapentin showed decreased motor activity, likely because of sedation. The data is limited in support of its use, but gabapentin has gained popularity in the management of feline chronic and neuropathic pain.

Biologics -

Feline-specific anti-NGF antibody is a promising therapy in management of chronic pain. Nerve growth factor contributes to peripheral and central sensitization, and its concentrations are increased in chronic painful conditions including OA. In one study in cats with OA, a single treatment with feline-specific anti-NGF antibody administered subcutaneously increased motor activity and improved CSOM scores up to 6 weeks. There are additional studies being conducted and stronger data may be soon available to veterinarians.

NSAIDs in the Management of Chronic Pain:

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Introduction

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are one of the most commonly used classes of drugs for managing chronic pain in small animals. There are several reasons for the dramatic increase in NSAID use in companion animals. There is now a better understanding of the need to manage acute and chronic pain in small animal medicine. Pain control is a very important mission for the practicing veterinarian. NSAIDs can be used to alleviate acute pain, either traumatic or surgically induced, and for chronic pain such as osteoarthritis and thud NSAIDs provide an effective means to accomplish this goal. FDA approved NSAIDs are very safe drugs; with only a small percentage of patients experiencing serious complications. However, these adverse events have achieved significant proportions based on the fact that so many dogs and cats are taking these agents each year—thus a small percentage becomes a very large number. Efficacy and toxicity are often individualistic and monitoring of each animal is mandatory in all cases. Choosing and monitoring NSAID usage is important; there are no definitive answers as to how this should be done. First it is wise to use products with a history of extensive clinical use. Use only one NSAID at a time and ensure correct dosing. Review the treatment plan frequently, and change to alternative NSAIDs if there is a poor response to therapy. Observe for potential toxicity as soon as administration is begun with increased vigilance and monitoring of high-risk patients. If indicated, establish renal and hepatic status of the patient prior to NSAID administration.

Mechanism of Action

Eicosanoids, which include the compounds known as prostaglandins, are derived from arachidonic acid (AA). It is the ability of NSAIDs to interfere with eicosanoid synthesis and the subsequent alteration of different physiologic systems that explains the numerous effects seen in the body with NSAID administration. Significant portions of the analgesic and anti-inflammatory clinical effects seen with NSAID administration are related to the inhibition of the COX enzyme isoforms. The COX enzymes initiate a complex cascade that results in the conversion of polyunsaturated acids to prostaglandins and thromboxane. With regard to pain, prostaglandins, primarily PGE2, contribute to the inflammatory response by causing vasodilation and enhancing the effects of other cytokines and inflammatory mediators. The production of PGE2 at various sites of inflammation appears to be mediated primarily by COX-2. Thus, when an inflammatory event occurs within the tissue, COX-2 enzyme production is induced, followed by an increase in prostaglandin concentrations. The selective inhibition of certain prostaglandins primarily produced by COX-2 should allow for the therapeutic analgesic and anti-inflammatory effects while greatly diminishing the unwanted side effects caused by COX-1 inhibition. However,

complete COX-2 inhibition is detrimental to many normal physiologic functions including the healing of gastric ulcers.

Site of Action

Data now support the concept that NSAIDs act on both the peripheral tissue injury site as well as at the level of the central nervous system (CNS). They inhibit the peripheral COX-2 enzyme to block the formation of prostaglandins such as PGE2 and PGI2, which function to dilate arterioles and sensitize peripheral nociceptors to the actions of mediators (e.g., histamine and bradykinin), which produce localized pain and hypersensitivity. PGE2 produced by COX-2 plays a pivotal role in sustaining acute pain sensation by increasing nociceptor cyclic AMP, which decreases the nociceptor threshold of activation. Centrally, COX-2-mediated prostaglandins such as PGE2 are involved in spinal nociception and central sensitization. COX-2 is expressed in the brain and spinal cord and is upregulated in response to traumatic injury and peripheral inflammation.

Recently there has been the introduction of an EP4 receptor antagonist to decrease the pain and inflammation in OA. Prostanoid EP4 receptors have been extensively implicated in mediating hyperalgesia and allodynia. All EP subtypes are expressed in sensory neurons, but EP4 may be regarded as the most important because it causes sensitization and is exclusively expressed in a subset of primary sensory dorsal root ganglia, which increases in subchronic inflammation. Data also suggests that PGE(2) inhibits proteoglycan synthesis and stimulates matrix degradation in OA chondrocytes via the EP4 receptor. Targeting EP4, rather than cyclooxygenase 2, could represent a future strategy for OA disease modification. Thus EP4 antagonists binds the EP4 receptor and blocks PGE_2 from exerting its biological effect. By blocking the binding of PGE_2 to its receptor, the signaling pathway for pain and inflammation is interrupted.

Clinical Applications

NSAIDs can be used to relieve pain in a variety of clinical settings. Efficacy and toxicity are often individualized, and individual monitoring is mandatory. There are numerous initiating pathways that produce pain that are not fully understood, and it would be naïve to think that all pathways will react in the same manner to different drugs. In addition, the heterogeneity of the patient response to a given NSAID in terms of efficacy and toxicity may be accounted for by slight variations in genetic expression or gene polymorphism of the COX enzymes known as the "COX continuum."

Choosing and Monitoring the Use of Nonsteroidal Anti-inflammatory Drugs

- Use products with history of clinical experience and good safety profiles.
- Use only one NSAID at a time, and ensure adequate dosage.

- Adapt therapy to suit patient requirements. Begin with the recommended dose for an extended period of time (at least 10 to 14 days) in animals with chronic pain.
- Avoid NSAIDs in patients with known contraindications to their use.
- Observe for potential toxicity. Increased vigilance and monitoring are required for at-risk patients. If indicated, establish renal and hepatic status of the patient before NSAID administration.

Contraindications

- Patients receiving any type of systemic corticosteroids.
- Patients receiving concurrent NSAIDs.
- Patients with documented renal or hepatic insufficiency or dysfunction.
- Patients with any clinical syndrome that creates a decrease in the circulating blood volume (e.g., shock, dehydration, hypotension, or ascites).
- Patients with active GI disease.
- Trauma patients with known or suspected significant active hemorrhage or blood loss.
- Pregnant patients or in females in which pregnancy is being attempted
- Patients with significant pulmonary disease. (This may be less important with COX-2–specific drugs).
- Patients with any type of confirmed or suspected coagulopathies. (This may be less important with COX-2–specific drugs).

Adverse Events

The most common problems associated with NSAID administration to dogs and cats involve the gastrointestinal (GI) tract. Signs may range from vomiting and diarrhea, including hematemesis and melena, to a silent ulcer which results in perforation. The true overall incidence of GI toxicity in dogs or cats treated with NSAIDS is unknown. Concurrent administration of other medications (especially other NSAIDs or corticosteroids), previous GI bleeding, or the presence of other systemic diseases may contribute to adverse reactions. Hepatotoxicosis caused by NSAIDs is generally considered to be idiosyncratic. 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 or hypotensive animals. This is especially important to remember with the increasing use of perioperative NSAIDs for pain management.

Other tissues that may be affected by NSAIDs are cartilage, bone and the cardiovascular system. Studies have demonstrated a variety of effects on proteoglycan synthesis when chondrocytes or cartilage explants are incubated with an NSAID in vitro. The most pronounced effects have been seen in chondrocytes from osteoarthritic joints, although a lesser effect has been demonstrated on normal cartilage. Aspirin is uniformly reported to cause inhibition of proteoglycan synthesis; conflicting data exist for other NSAIDs, such as etodolac, showing both potential negative and positive effects; and there is a final group, including meloxicam, piroxicam, tepoxalin, and carprofen, in which no effect or even some increased synthesis of proteoglycan has been noted. The significance of these in vitro findings remains unclear, and the clinical significance of these data in the clinical setting with naturally occurring disease is unknown. In regard to bone healing, it is interesting to note that prostaglandins also play an important role in bone repair and normal bone homeostasis. Experimental studies support the hypothesis that both nonspecific and specific COX inhibitors (COX-1 sparing) do impair bone healing. These statements are based on rabbit, rat, and mouse induced fracture models that show that COX-1–sparing agents do alter bone healing. However, the most recent data confirm that after cessation of NSAIDs, fracture healing returns to its normal rate, and therefore judicious use of postoperative NSAIDs can be recommended. Stated another way, any potential adverse effects must be weighed against potential benefits that include but are not limited to improved analgesia and earlier return to function (both mobilization of the limb and the patient and weight bearing), and data support use of NSAIDs in the immediate postoperative period as long as the administration is not continuous for several weeks. Finally, NSAIDs can occasionally have significant cardiovascular effects. Nonselective NSAIDs inhibit the platelet COX-1 enzyme and cause a significant decrease in the amount of thromboxane A2 (TXA2) produced by activated platelets. Thromboxane is an important promoter of platelet aggregation in most dogs and is released by activated platelets to recruit additional platelets to the site of vessel injury. Thromboxane is also a potent vasoconstrictor. A decrease in thromboxane release can result in prolongations of primary hemostasis. COX-1–sparing (COX-2–selective inhibitor) drugs do not have this effect on thromboxane production and likely do not clinically affect primary hemostasis, depending on the study methodology. The actions of thromboxane are balanced at the vessel level by the presence of prostacyclin (PGI2), which is produced by COX enzymes in the vascular endothelial cells. PGI2 is a strong inhibitor of platelet aggregation and also results in vasodilation. In the presence of endothelial inflammation (such as that caused by atherosclerotic plaques), the expression of COX-2 in the endothelial cells increases and may produce the majority of prostacyclin in that area. When COX nonselective NSAIDs are administered, the expression of both thromboxane from platelets and PGI2 from endothelial cells is decreased, preserving the balance. In certain circumstances of endothelial inflammation (e.g., with atherosclerosis), specific COX-2 inhibitors may decrease the endothelial production of PGI2 (mainly from COX-2) without a concomitant

decrease in platelet thromboxane (produced only by COX-1), and consequently may result in the development of a hypercoagulable state.

Recap of specific NSAIDs

The approved NSAIDs available to the clinician vary considerably around the world. It is very important for practitioners to remember that the clinical response to a particular drug is quite individualistic. Dogs may respond favorably to one product and not another, so if a NSAID is indicated in a case and the first product used does not achieve a positive clinical response, do not forsake NSAIDs but try a different product.

Carprofen

Carprofen is approved, both in oral and injectable formulations, to treat pain and inflammation associated with osteoarthritis (OA). Carprofen has improved limb function in clinical trials of dogs with naturally occurring osteoarthritis. Three long-term studies (84 days and 120 days) found that carprofen was well tolerated and subjectively dogs appeared to improve over the treatment period. In certain countries, a single injectable dose in cats is approved for pain. While there is ample data to support single dose use for perioperative pain, repetitive dosing in cats is not recommended until additional safety and efficacy data is produced with multiple dose protocols.

Deracoxib

Deracoxib is approved in an oral formulation in dogs for treatment of pain and inflammation associated with OA and postoperative pain associated with orthopedic surgery. It has been demonstrated to provide effective relief of pain in clinical osteoarthritis trials in dogs in a study which has never been published in a peer reviewed journal but has been presented in abstract form. The same situation is present with a study showing effectiveness in relieving pain related to orthopedic surgery.

Firocoxib

Firocoxib is approved, as an oral formulation, with an indication for the management of pain and inflammation associated with OA in dogs. Clinically it has been shown to improve limb function in dogs with osteoarthritis. Clinical trials suggest that firocoxib may have some superiority based on owner and veterinarian subjective evaluations with regard to lameness resolution when compared to carprofen and etodolac in dogs with OA. Long-term dosing of firocoxib showed continued improvements over the year of treatment.

Mavacoxib

Mavacoxib is approved by the European Union as an oral formulation in dogs for treatment of pain and inflammation associated with OA. Mavacoxib is a long acting agent with an approved

dosing regimen consists of a loading dose repeated at 14 days and thereafter at dosing intervals of 1 month.

Meloxicam

Meloxicam has been approved for use in dogs for the control of pain and inflammation associated with OA and is available in oral, transmucosal oral mist, and parenteral formulations. With the amount and quality of the published data available for use of meloxicam for management of acute postsurgical and well as chronic OA pain in dogs.

Meloxicam is approved for use in cats, but that approval is limited to a single dose to control pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in the US. Long term use of meloxicam for the treatment of musculoskeletal pain in cats is approved in several countries. Use in cats from 5 days to indefinite dosing to provide analgesia for locomotor disorders including OA has been described at several different dosing levels (0.01 to 0.05 PO mg/kg) daily.While these data exist, clinical efficacy is supported by data generated from studies using the 0.05 mg/kg dose PO every 24 hours. At lower dosing regimens (0.01 to 0.03mk/kg PO q 24 hours), meloxicam has been shown to be well tolerated and safe in cats including cats with chronic renal dysfunction.

Robenacoxib

Robenocoxib is approved for only dogs or both dogs and cats depending on the country. Indications in the dog are for treatment of pain and inflammation associated with orthopedic or soft tissue surgery as well as the treatment of pain and inflammation associated with chronic osteoarthritis (depending on the country).

In the cat, approved indications (depending on the country) may include treatment of postoperative pain and inflammation associated with orthopedic and soft tissue surgeries as well as the acute pain and inflammation associated with musculoskeletal disorders. Length of approved treatment times for robenacoxib in the cat varies from 3 to 11 days.

Washout period between NSAIDs.

A question that is commonly asked by clinicians is whether or not a washout period is needed when switching NSAIDs. Several sources, including crowd sourcing websites, conference proceedings, pharmaceutical company promotional materials as well as journal articles, have advocated a washout period of varying lengths (1 to 7 days) when changing NSAIDs for presumed lack of efficacy. These recommendations are not based on clinical data but rather are derived from extrapolations of pharmacokinetic data and conservative speculation. There are several different situations that need to be addressed when discussing how to switch NSAIDs in our clinical patients. The first situation is a switch after a single dose of a perioperative parenteral NSAID (e.g. carprofen or meloxicam) followed by an oral NSAID the

following day. The only data to use in this situation is a study of normal healthy dogs that were given parenteral (sub-cutaneous) carprofen followed by deracoxib orally 24 hours later and repeat for four days. This was one arm of the study and when compared to continuous carprofen (sub-cutaneous and oral) or placebo there were no differences in clinical findings or gastric lesions. Thus from this limited data it appears that it may be safe to switch from a single injection of one drug to an oral formulation the next day if using another product. However, without testing injectable meloxicam and the other oral products with meloxicam or carprofen one cannot be definitive about these treatment recommendations.

The second situation is switching NSAIDs for perceived lack of a response and perceived efficacy. This is a difficult question that often faces a clinician and here is where there is a significant variation in recommendations. Many reports discuss waiting 5 half-lives of the first drug before initiating the second drug. The only clinical data which may shed light on this situation is a report of switching to firocoxib from another NSAID, which showed no increase in documented side effects whether firocoxib was started the next day up to day seven from stopping the original drug. These data would again suggest that a washout period is not necessary, but most clinicians follow the recommendation discontinuing a NSAID for 1 to 7 days before initiating another drug. The final situation is transitioning to or from aspirin. If aspirin is the initial drug it has been recommended that a minimum of a seven day washout period be followed before starting another NSAID, to provide time for platelet regeneration due to aspirin's irreversible effects on platelets. There is no clinical data to support this recommendation. The second situation could occur if for some reason a dog is on a product that is COX-1 sparing (a primary COX-2 inhibitor) and is then changed to aspirin, a seven day washout is recommended due to the gastric adaptation and production of aspirin-triggered lipoxins(ATLs). The concern here is that when a patient is on aspirin, ATLs are produced and have been shown to exert protective effects in the stomach by diminishing gastric injury most likely via release of nitric oxide from the vascular endothelium. However, concurrent administration of COX-1 sparing drugs with aspirin results in the complete inhibition of ATLs and can potentially cause significant exacerbation of gastric mucosal injuries. It is important to remember that the formation of ATLs has yet to be proven in the dog.